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(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM CORPORATION [US/US]; 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)* : JOHNSON, Randall, Keith [US/US]; 71 Llanfiar Circle, Ardmore, Pennsylvania 19003 (US).

(74) Agents: STERCHO, Yuriy, P. et al.; SmithKline Beecham Corporation, Corporate Patents, UW2220, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).

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(54) Title: TREATMENT OF NON-SMALL CELL LUNG CARCINOMA

(57) Abstract

A method of treating non-small cell lung carcinoma in a human afflicted therewith which comprises administering to such human an effective amount of a compound of the water soluble camptothecin analog class.

FOR THE PURPOSES OF INFORMATION ONLY

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TREATMENT OF NON-SMALL CELL LUNG CARCINOMA

BACKGROUND OF THE INVENTION

This invention relates to a method of treating non-small cell lung carcinoma in a human afflicted therewith which comprises administering to such human an effective amount of a compound of the water soluble camptothecin analog class, such as topotecan.

The structure of the DNA helix within eukaryotic cells imposes certain topological problems that the cellular apparatus must solve in order to use its genetic material as a template. The separation of the DNA strands is fundamental to cellular processes such as DNA replication and transcription. Since eukaryotic DNA is organized into chromatin by chromosomal proteins, the ends are constrained and the strands cannot unwind without the aid of enzymes that alter topology. It has long been recognized that the advancement of the transcription or replication complex along the DNA helix would be facilitated by a swivel point which would relieve the torsional strain generated during these processes.

Topoisomerases are enzymes that are capable of altering DNA topology in eukaryotic cells. They are critical for important cellular functions and cell proliferation. There are two classes of topoisomerases in eukaryotic cells, type I and type II.

Topoisomerase I is a monomeric enzyme of approximately 100,000 molecular weight. The enzyme binds to DNA and introduces a transient single-strand break, unwinds the double helix (or allows it to unwind), and subsequently reseals the break before dissociating from the DNA strand.

Camptothecin, a water-insoluble alkaloid produced by trees indigenous to China and India, and a few other congeners thereof, are the only class of compounds known to inhibit topoisomerase I.

Camptothecin and other topoisomerase I inhibiting congeners have not proven to be attractive for clinical drug development as cytolytic agents because of lack of clinical efficacy, unacceptable dose-limiting toxicity, unpredictable toxicity, poor aqueous solubility, and/or unacceptable shelf life stability.

Therefore, there is a need for topoisomerase I inhibiting agents which avoid the aforementioned undesirable features of camptothecin and related topoisomerase I inhibiting congeners. Topotecan, or any compound of the water soluble camptothecin analog class, is a specific inhibitor of DNA topoisomerase I which fulfills such need.

SUMMARY OF THE INVENTION

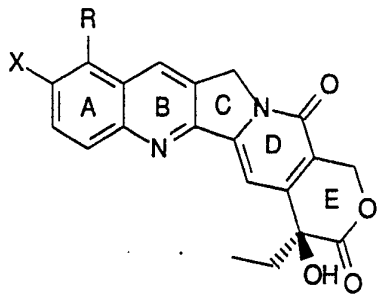
This invention relates to a method of treating non-small cell lung carcinoma in a human afflicted therewith which comprises administering to such human an effective amount of a compound of the water soluble camptothecin analog class.

This invention also relates to a method of treating non-small cell lung carcinoma in a human afflicted therewith which comprises administering to such human an effective amount of topotecan.

DETAILED DESCRIPTION OF THE INVENTION

By the term "a compound of the water soluble camptothecin analog class" is meant any compound claimed in U.S. Patent Number 5,004,758, the entire disclosure of which is hereby incorporated by reference. The preparation of any compound of the water soluble camptothecin analog class (including pharmaceutically acceptable salts, hydrates and solvates thereof) as well as the preparation of oral and parenteral pharmaceutical compositions comprising a compound of the water soluble

camptothecin analog class and an inert, pharmaceutically acceptable carrier or diluent, is extensively described in U.S. Patent Number 5,004,758. The same extensive description is found in European Patent Application Number 88311366.4, published on June 21, 1989 as Publication Number EP 0 321 122, the entire disclosure of which is hereby incorporated by reference. Preferred compounds of the water soluble camptothecin analog class include those compounds of the formula:



wherein:

a) X is hydroxy and R is trimethylammoniummethyl;

b) X is hydroxy and R is N-methylpiperazinylmethyl;

c) X is hydroxy and R is N-methylanilinomethyl;

d) X is hydroxy and R is cyclohexylaminomethyl;

e) X is hydroxy and R is N,N-dimethylaminoethyloxymethyl;

f) X is hydroxy and R is cyclopropylaminomethyl;

g) X is hydroxy and R is morpholinomethyl;

h) X is hydroxy and R is aminomethyl; and

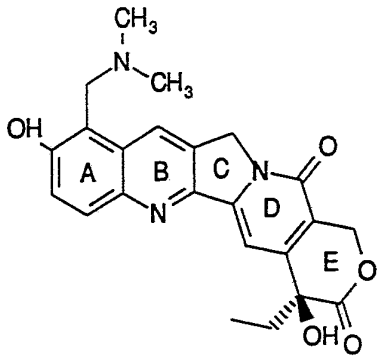
i) X is hydroxy and R is cyanomethyl; and

j) X is hydroxy and R is dimethylaminomethyl

or any pharmaceutically acceptable salts, hydrates and solvates thereof.

Topotecan is the most preferred compound of the water soluble camptothecin analog class. By the term "topotecan" as used herein is meant the compound of the

formula:



(S)-9-dimethylaminomethyl-10-hydroxycamptothecin and any pharmaceutically acceptable salt, hydrate or solvate thereof. Topotecan's chemical name is (S)-10[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolone-3,14(4H,12H)-dione.

Topotecan is water-soluble by virtue of the presence of the basic side-chain at position 9 which forms salts with acids. Preferred salt forms of topotecan include the hydrochloride salt, acetate salt and methanesulfonic acid salt. A alkali metal salt form of the carboxylate formed on alkaline hydrolysis of the E-ring lactone of topotecan would also yield a soluble salt, such as the sodium salt.

The preparation of topotecan (including pharmaceutically acceptable salts, hydrates and solvates thereof) as well as the preparation of oral and parenteral pharmaceutical compositions comprising topotecan and an inert, pharmaceutically acceptable carrier or diluent, is extensively described in U.S. Patent Number 5,004,758. The same extensive description is found in European Patent Application Number 88311366.4, published on June 21, 1989 as Publication Number EP 0 321 122.

This invention relates to a method of treating non-small cell lung carcinoma in a human afflicted

therewith which comprises administering to such human an effective amount of a compound of the water soluble camptothecin analog class. One preferred aspect of this invention relates to a method of treating non-small cell lung carcinoma in a human afflicted therewith which comprises administering to such human an effective amount of topotecan.

By the term "non-small cell lung carcinoma" as used herein is meant any of the three subtypes thereof, i.e., adenocarcinoma of the lung, squamous cell carcinoma of the lung and large cell carcinoma of the lung.

By the term "treating non-small cell lung carcinoma" as used herein is meant the inhibition of the growth of non-small cell lung carcinoma cells. Preferably such treatment also leads to the regression of tumor growth, i.e., the decrease in size of a measurable tumor. Most preferably, such treatment leads to the complete regression of the tumor.

By the term "administering" is meant parenteral or oral administration. By "parenteral" is meant intravenous, subcutaneous and intramuscular administration.

By the term "effective amount of a compound of the water soluble camptothecin analog class" and "effective amount of topotecan" as used herein is meant a course of therapy which will result in treating non-small cell lung carcinoma. It will be appreciated that the actual preferred course of therapy will vary according to, inter alia, the mode of administration, the particular formulation of a compound of the water soluble camptothecin analog class (such as topotecan) being utilized, the mode of administration and the particular host being treated. The optimal course of therapy for a given set of conditions can be ascertained by those skilled in the art using conventional course of therapy determination tests in view of the information

set out herein, as well as the information outlined in U.S. Patent Number 5,004,758. The same information is found in European Patent Application Number 88311366.4, published on June 21, 1989 as Publication Number EP 0 321 122.

For parenteral administration of a compound of the water soluble camptothecin analog class, the course of therapy generally employed is from about 0.5 to about 25.0 mg/m^2 of body surface area per day for about one to about five consecutive days. More preferably, the course of therapy employed is from about 1.0 to about 2.5 mg/m^2 of body surface area per day for about five consecutive days. Most preferably, the course of therapy employed is from about 1.5 to about 2 mg/m^2 of body surface area per day for about five consecutive days. Preferably, the course of therapy is repeated at least once at about a seven day to about a twenty-eight day interval (from the date of initiation of therapy) depending upon the initial dosing schedule and the patient's recovery of normal tissues. Most preferably, the course of therapy continues to be repeated based on tumor response.

Preferably, the parenteral administration will be by short (e.g., 30 minute) or prolonged (e.g., 24 hour) intravenous infusion. More preferably, the topotecan will be administered by a 30 minute intravenous infusion.

At this time, it is believed that the most preferred course of parenteral therapy to be employed with topotecan for a previously non-treated or lightly pretreated patient is an initial course of therapy of 1.5 mg of topotecan/m^2 of body surface area per day administered by short intravenous infusion for five consecutive days. When the patient has recovered sufficiently from the drug-related effects of this initial course, an additional course of therapy of 2.0 mg of topotecan/m^2 of body surface area per day is

administered by short intravenous infusion for five consecutive days, to be repeated based on tumor response.

At this time, it is believed that the most preferred course of parenteral therapy to be employed with topotecan for a heavily pretreated patient is an initial course of therapy of 1.0 mg of topotecan/m^2 of body surface area per day administered by short intravenous infusion for five consecutive days. When the patient has recovered sufficiently from the drug-related effects of this initial course, an additional course of therapy of 1.5 mg of topotecan/m^2 of body surface area per day is administered by short intravenous infusion for five consecutive days, such course of therapy to be repeated based on tumor response.

For oral administration of a compound of the water soluble camptothecin analog class, the course of therapy generally employed is from about 1.0 to about 50.0 mg/m^2 of body surface area per day for about one to five consecutive days. More preferably, the course of therapy employed is from about 1.5 to about 5.0 mg/m^2 of body surface area per day for about five consecutive days. Preferably, the course of therapy is repeated at least once at about a seven day to about a twenty-eight day interval (from the date of initiation of therapy) depending upon the initial dosing schedule and the patient's recovery of normal tissues. Most preferably, the course of therapy continues to be repeated based on tumor response.

Clinical Pharmaceutical Information

Topotecan is currently undergoing Phase I clinical investigation. The following pharmaceutical information is being supplied to the clinicians:

How supplied - As a vial containing 5 mg (of the base) with 100 mg mannitol. The pH is adjusted to 3.0 with HCl/NaOH. Lyophilized powder is light yellow

in color. Intact vials should be stored under refrigeration (2-8 degrees Centigrade).

Solution Preparation -When the 5 mg vial is reconstituted with 2 ml of Sterile Water for Injection, USP, each ml will contain 2.5 mg of topotecan as the base and 50 mg of mannitol, USP. Topotecan must not be diluted or mixed with buffered solutions because of solubility and stability considerations.

Stability - Shelf life surveillance of the intact vials is ongoing. Because the single-use lyophilized dosage form contains no antibacterial preservatives, it is advised that the reconstituted solution be discarded eight hours after initial entry into the vial. Futher dilutions of the reconstituted solution to concentrations of 0.02 mg/ml and 0.1 mg.ml in 5% Dextrose Injection, USP, ("D5W") or 0.9% Sodium Chloride Injection, USP, ("NS") in plastic bags stored at room temperature yielded the following stability results:

Percentage of Initial Topotecan Remaining in Solution

Diluent	Time (hrs)	Concentration 0.02 mg/ml	0.1 mg/ml
D5W	0	100.00	100.00
	6	99.29	99.68
	24	102.30	98.16
	48	101.98	97.91
NS	0	100.00	100.00
	6	98.58	97.71
	24	96.01	98.30
	48	102.03	98.35

Topotecan diluted in saline (10 ug/ml or 500 ug/ml) or dextrose (6.7 ug/ml or 330 ug/ml) is stable in a hang-bag for 24 hours with at least 95% recovery.

Treatment dose - The treatment dose is to be diluted in a final volume of 150 ml of Sodium Chloride Injection, USP (without preservatives) and administered over a 30 minute period. The treatment dose is to be

kept under refrigeration and protected from light and it is to be used within 24 hours.

Utility

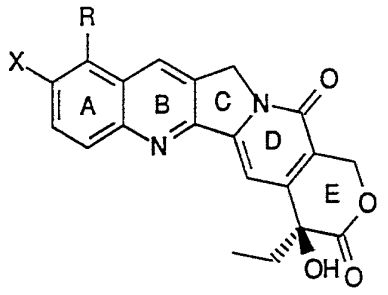
One human patient with metastatic non-small cell lung carcinoma, who was refractory to pretreatment with VP-16 (etoposide) and cisplatin, received a course of therapy comprising intravenous administration of 1.5 mg of topotecan/m^2 of body surface area per day for five consecutive days. This course of therapy was repeated at least five more times at twenty-one day intervals (from the date of initiation of therapy) for a total of at least six to four treatments. Tumor size regression was evaluated by CAT (computerized axial tomography) scan. After the above-outlined six treatment regimen, a complete regression of the disease was observed, i.e., all tumors had disappeared and no evidence of clinical disease was present.

In addition, a temporary response (measurable tumor size regression) was observed in a patient with non-small cell lung carcinoma who had received at least one course of therapy comprising intravenous administration of 1.5 mg of topotecan/m^2 of body surface area per day for five consecutive days. Such patient had previously received radiation and failed to respond to the investigational agent ipomeanol.

CLAIMS

What is claimed is:

1. A method of treating non-small cell lung carcinoma in a human afflicted therewith which comprises administering to such human an effective amount of a compound of the formula:



wherein:

a) X is hydroxy and R is trimethylammoniummethyl;

b) X is hydroxy and R is N-methylpiperazinylmethyl;

c) X is hydroxy and R is N-methylanilinomethyl;

d) X is hydroxy and R is cyclohexylaminomethyl;

e) X is hydroxy and R is N,N-dimethylaminoethyloxymethyl;

f) X is hydroxy and R is cyclopropylaminomethyl;

g) X is hydroxy and R is morpholinomethyl;

h) X is hydroxy and R is aminomethyl;

i) X is hydroxy and R is cyanomethyl; or

j) X is hydroxy and R is dimethylaminomethyl

or any pharmaceutically acceptable salts, hydrates and solvates thereof.

2. The method of Claim 1 wherein the administration is oral.

3. The method of Claim 1 wherein the administration is parenteral.

4. The method of Claim 3 wherein the course of therapy employed is from about 0.5 to about 25.0 mg/m^2

of body surface area per day for about one to about five consecutive days.

5. The method of Claim 4 wherein the course of therapy employed is from about 1.0 to about 2.5 mg/m^2 of body surface area per day for about five consecutive days.

6. The method of Claim 5 wherein the course of therapy employed is from about 1.5 to about 2 mg/m^2 of body surface area per day for about five consecutive days.

7. The method of Claim 4 wherein the course of therapy is repeated at least once at about a seven day to about a twenty-eight day interval.

8. The method of Claim 5 wherein the course of therapy is repeated at least once at about a seven day to about a twenty-eight day interval.

9. The method of Claim 6 wherein the course of therapy is repeated at least once at about a seven day to about a twenty-eight day interval.

10. The method of Claim 2 wherein the administration is via short or long intravenous infusion.

11. The method of Claim 10 wherein the administration is via a 30 minute intravenous infusion.

12. The method of Claim 10 wherein the administration is via a 24 hour intravenous infusion.

13. The method of Claim 3 wherein the course of therapy employed is from about 1.0 to about 50.0 mg/m^2 of body surface area per day for about one to about five consecutive days.

14. The method of Claim 13 wherein the course of therapy employed is from about 1.5 to about 5.0 mg/m^2 of body surface area per day for about five consecutive days.

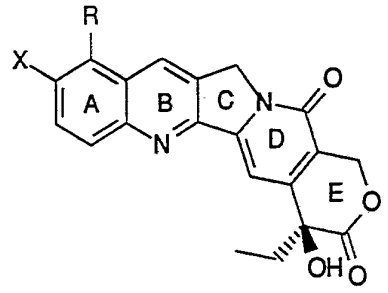
15. The method of Claim 13 wherein the course of therapy is repeated at least once at about a seven day to about a twenty-eight day interval.

16. The method of Claim 14 wherein the course of therapy is repeated at least once at about a seven day to about a twenty-eight day interval.

17. The method of Claim 1 wherein the compound is topotecan.

18. The method of Claim 10 wherein the compound is topotecan.

19. Use of a compound of of the formula:



wherein:

a) X is hydroxy and R is trimethylammoniummethyl;

b) X is hydroxy and R is N-methylpiperazinylmethyl;

c) X is hydroxy and R is N-methylanilinomethyl;

d) X is hydroxy and R is cyclohexylaminomethyl;

e) X is hydroxy and R is N,N-dimethylaminoethyloxymethyl;

f) X is hydroxy and R is cyclopropylaminomethyl;

g) X is hydroxy and R is morpholinomethyl;

h) X is hydroxy and R is aminomethyl;

i) X is hydroxy and R is cyanomethyl; or

j) X is hydroxy and R is dimethylaminomethyl

or any pharmaceutically acceptable salts, hydrates and solvates thereof, in the manufacture of a medicament for use in the treatment of non-small cell lung carcinoma.

20. The use of Claim 19 wherein the medicament is adapted for oral administration.

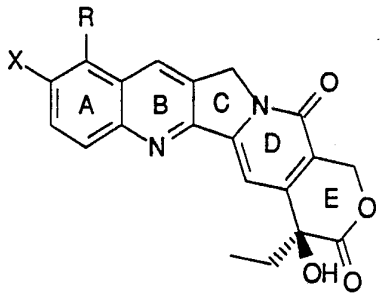
21. The use of Claim 19 wherein the medicament is adapted for parenteral administration.

22. The use of Claim 19 wherein the compound is topotecan.

23. The use of Claim 20 wherein the compound is topotecan.

24. The use of Claim 21 wherein the compound is topotecan.

25. A pharmaceutical composition for use in the treatment of non-small cell lung carcinoma in a human afflicted therewith comprising a compound of of the formula:



wherein:

a) X is hydroxy and R is trimethylammoniummethyl;

b) X is hydroxy and R is N-methylpiperazinylmethyl;

c) X is hydroxy and R is N-methylanilinomethyl;

d) X is hydroxy and R is cyclohexylaminomethyl;

e) X is hydroxy and R is N,N-dimethylaminoethyloxymethyl;

f) X is hydroxy and R is cyclopropylaminomethyl;

g) X is hydroxy and R is morpholinomethyl;

h) X is hydroxy and R is aminomethyl;

i) X is hydroxy and R is cyanomethyl; or

j) X is hydroxy and R is dimethylaminomethyl or any pharmaceutically acceptable salts, hydrates and solvates thereof.

26. The composition of Claim 25 which is adapted for oral administration.

27. The composition of Claim 25 which is

adapted for parenteral administration.

28. The composition of Claim 25 wherein the compound is topotecan.

29. The composition of Claim 26 wherein the compound is topotecan.

30. The composition of Claim 27 wherein the compound is topotecan.

31. The method of Claim 1 wherein the non-small cell lung carcinoma is adenocarcinoma of the lung.

32. The method of Claim 1 wherein the non-small cell lung carcinoma is squamous cell carcinoma of the lung.

33. The method of Claim 1 wherein the non-small cell lung carcinoma is large cell carcinoma of the lung.

34. The use of Claim 19 wherein the non-small cell lung carcinoma is adenocarcinoma of the lung.

35. The use of Claim 19 wherein the non-small cell lung carcinoma is squamous cell carcinoma of the lung.

36. The method of Claim 19 wherein the non-small cell lung carcinoma is large cell carcinoma of the lung.

37. The method of Claim 25 wherein the non-small cell lung carcinoma is adenocarcinoma of the lung.

38. The method of Claim 25 wherein the non-small cell lung carcinoma is squamous cell carcinoma of the lung.

39. The method of Claim 25 wherein the non-small cell lung carcinoma is large cell carcinoma of the lung.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US92/01034

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC (5): A61K 31/535; A61K 31/495; A61K 31/44

U.S.Cl.: 514/233.2; 514/253; 514/283

II FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	514/233.2; 514/253; 514/283

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

CHEMICAL ABSTRACTS; CHEMICAL SUBSTANCES 1972 - PRESENT

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X,P	US, A, 5,004,758 (BOEHM ET AL.) 02 April 1991 See the entire document.	1-39

[10] 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

"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

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
04 June 1992	23 JUN 1992

International Searching Authority	Signature of Authorized Officer
ISA/US	NGUYEN NGOC-AU INTERNATIONAL DIVISION Jerome D. Goldberg

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers . . because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers . . , 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 [13], specifically:

3. ☐ Claim numbers_____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

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 of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ 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 claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.