(11) Application No. AU 2001255475 B2

(19) AUSTRALIAN PATENT OFFICE

(54) Title
Method of reducing side effects of chemotherapy in cancer patients

(51)[6] International Patent Classification(s)
A61K 38/22 (2006.01) A61K 31/00 20060101ALI20060101BHAU
A61K 31/00 (2006.01) A61K 33/00 20060101ALI20060101BHAU
A61K 33/00 (2006.01) A61K 38/00 20060101ALI20060101BHAU
A61K 38/00 (2006.01) A61K 38/22 20060101AFI20060101BHAU
PCT/US01/12696

(21) Application No: 2001255475 (22) Application Date: 2001.04.19

(87) WIPO No: WO01/82949

(30) Priority Data

(31) Number	(32) Date	(33) Country
09/561,917	2000.05.01	US

(43) Publication Date : 2001.11.12
(43) Publication Journal Date : 2002.01.31

(71) Applicant(s)
SciClone Pharmaceuticals, Inc.

(72) Inventor(s)
Tam, Vincent Chung-Yin; Quan, Maggie Jie; Rudolph, Alfred R.

(74) Agent/Attorney
Wray & Associates, PO Box Z5466 St Georges Terrace, Perth, WA, 6831

(56) Related Art
Ohta Y et al., 1985
Salvati, F et al., 1996
Garachi, E et al., 1995
Silecchia, G et al., 1999
Ishitsuka, H et al., 1984

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 November 2001 (08.11.2001)

PCT

(10) International Publication Number
WO 01/82949 A2

(51) International Patent Classification[7]: A61K 38/22 // (A61K 38/22, 31:00) (A61K 38/22, 33:00) (A61K 38/22, 38:00)

(21) International Application Number: PCT/US01/12696

(22) International Filing Date: 19 April 2001 (19.04.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/561,917 1 May 2000 (01.05.2000) US

(71) Applicant: SCICLONE PHARMACEUTICALS, INC. [US/US]; 901 Mariners Island Boulevard, San Mateo, CA 94404 (US).

(72) Inventors: RUDOLPH, Alfred, R.; 14142 Liddicoat Drive, Los Altos Hills, CA 94022 (US). TAM, Vincent, Chung-Yin; 35, Ventris Road, Happy Valley, Hong Kong (CN). QUAN, Maggie, Jie; Room 502, No. 16, Lane 336, E Mei Road, Shanghai 200080 (CN).

(74) Agents: REPPER, George, R. et al.; Rothwell, Figg, Ernst & Manbeck, P.C., Suite 701-E, 555 13th Street, N.W., Washington, DC 20004 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/82949 A2

(54) Title: METHOD OF REDUCING SIDE EFFECTS OF CHEMOTHERAPY IN CANCER PATIENTS

(57) Abstract: A method for reducing the severity of chemotherapy side effects in cancer patients by administering thymosin α_1 in conjunction with the administration of a chemotherapy agent to the patient. As a result of the reduction of post-chemotherapy side effects, patients experience an increase in the quality of life.

METHOD OF REDUCING SIDE EFFECTS OF CHEMOTHERAPY IN CANCER PATIENTS

FIELD OF THE INVENTION

The present invention relates to improved treatment of cancer in animals, including humans, by reducing the side effects of chemotherapy.

BACKGROUND OF THE INVENTION

Cancers are a leading cause of death in animals and humans. The leading cancer therapies today are surgery, radiation and chemotherapy. In spite of advances in the field of cancer treatment, each of these known therapies has serious side effects. For example, surgery disfigures the patient or interferes with normal bodily functions. Chemotherapy or radiation therapies cause patients to experience acute debilitating symptoms including nausea, vomiting, diarrhea, hypersensitivity to light, hair loss, etc. The side effects of these cytotoxic compounds frequently limit the frequency and dosage at which they can be administered.

Chemotherapeutic agents have been found useful in treating cancer in humans. Broadly classified as antineoplastics, chemotherapeutic agents found to be of assistance in the suppression of tumors include but are not limited to alkylating agents (e.g., nitrogen mustards), antimetabolites (e.g., pyrimidine analogs), radioactive isotopes (e.g., phosphorous and iodine), hormones (e.g., estrogens and adrenocorticosteroids), miscellaneous agents (e.g., substituted ureas) and natural products (e.g., vinca alkyloids and antibiotics). Although the preceding compounds are not curative agents, they are widely recognized in the medical profession as useful in the suppression, palliation, retardation and control of malignant tumors. While these compounds have been found to be effective and are in general clinical use as antiproliferative agents, there are well recognized drawbacks associated with their administration. The alkylating agents have marked cytotoxic action and the ability of these drugs to interfere with normal mitosis and cell division can be lethal. The antimetabolites can lead to anorexia, progressive weight loss, depression, and coma. Prolonged administration of antimetabolites can result in serious changes in bone marrow. Both the alkylating agents and the antimetabolites generally have a depressive effect on the immunosuppressive system. Prolonged administration of natural products such as vinca alkyloids can also result in bone marrow depression. Hydroxy urea and other chemically derived agents can lead to rapid reduction in levels of adrenocorticosteriods and their metabolites. The administration of hormonal compounds or radioactive isotopes is also

undesirable from the viewpoint of inflicting damage on the immunosuppressive system and thereby disabling the body's defenses against common infections. In most instances, it would be preferable to employ a chemotherapeutic agent which is effective in controlling, retarding, or suppressing the growth of malignant tumors while simultaneously acting to stimulate the patient's immune system.

SUMMARY OF THE INVENTION

In accordance with the present invention, a method is provided in which the side effects of chemotherapy in cancer patients are reduced by administering thymosin α_1 ("Tα_1") in conjunction with the administration of the chemotherapy agent to the patient. The reduction in the severity of post-chemotherapy side effects increases the quality of life experienced by patients receiving chemotherapy.

DETAILED DESCRIPTION OF THE INVENTION

It is known that the thymus produces a family of polypeptides termed thymosin and perhaps several other thymic hormones and/or factors which play an important role in the maturation, differentiation and function of T-cells. Thymosin has been found to induce T-cell differentiation and enhance immunological functions in genetically athymic mice, in adult thymectisized mice and in NZB mice with severe autoimmune reactions, in tumor bearing mice and in mice with casein-induced amyloidosis.

Thymosin α_1, an acidic polypeptide isolated from thymosin fraction 5 is an immunomodulator that acts primarily by enhancing T-cell function and also has been shown to have direct anti-cancer effects. Thymosin α_1 has been found to stimulate T-cell maturation, differentiation and function.

It has been previously documented that thymosin α_1 reduces the incidence and severity of post-chemotherapy infections. It has now been found that the use of thymosin α_1 in conjunction with the administration of antineoplastics (chemotherapeutic agents) significantly improves the cancer patient's quality of life by reducing nausea, vomiting, loss of appetite, inability to sleep, decline in overall feeling, reduction in daily activity, fatigue and depression. The administration of thymosin α_1 does not appear to result in any side effects.

The mechanism by which thymosin α_1 acts to improve the patient quality of life is not yet known. Without being bound to any particular theory, one possibility may relate to the apparent ability of thymosin α_1 to block neurotransmitter receptors. It is believed that most

chemotherapeutic agents activate the chemoreceptor trigger zone (CTZ) and that the CTZ chemotherapy interaction triggers the release of neurotransmitters that activate the vomiting center. CTZ neurotransmitters that are thought to cause emesis include but are not limited to, dopamine, serotonin, histamine, norepinephrine, apomorphine, neurotensin, vasoactive intestinal polypeptide (VIP). In vitro and in vivo studies, have shown that thymosin α_1 has a VIP receptor blocking effect. This may explain why thymosin α_1 can control vomiting in patients whose vomiting could not be controlled by 5-HT blockers.

The increase in quality of life may be due to thymosin α_1's ability to control GI adverse effects like nausea and vomiting through the above described VIP receptor blocking effect or it could be the result of a reduction of low grade, clinically undetectable infections or some combination thereof.

In one embodiment of the present invention, the thymosin α_1 is administered prior to the administration of the chemotherapy. The thymosin α_1 may be administered on a single day or be administered on several days prior to the chemotherapy.

In another embodiment of the invention, the thymosin α_1 is administered following the administration of the antineoplastic agent. In this embodiment, the thymosin α_1 may be administered once or several times following the chemotherapy. This administration may take place on a single day or on a series of days following the administration of the antineoplastic agent.

In another embodiment of the invention, thymosin α_1 is administered prior to and subsequent to the administration of the antineoplastic agent. This administration may take place on one or multiple days prior to and one or multiple days subsequent to the chemotherapy.

In one preferred embodiment, thymosin α_1 is administered to cancer patients once each day on four days immediately preceding the administration of the antineoplastic agent and once on day 2 and on day 4 following chemotherapy.

$T\alpha_1$ can be administered in any suitable way, such as by injection, infusion, or transcutaneously. Other methods of administration may also be possible, such as orally as a liquid or solid dosage form. In preferred embodiments $T\alpha_1$ is injected.

Thymosin α_1 may be administered at any suitable dosage level, e.g., within a range of about 0.1 - 3 mg. In preferred embodiments, thymosin α_1 is administered via injection at a dosage of about 1.6 mg s.c.

Thymosin α_1 can be administered to reduce side effects of any suitable antineoplastic agents, including one or more antineoplastic agent selected from the group consisting of alkylating agents (e.g., nitrogen mustards), antimetabolites (e.g., pyrimidine analogs), radioactive

isotopes (e.g., phosphorous and iodine), hormones (e.g., estrogens and adrenocorticosteroids), miscellaneous agents (e.g., substituted ureas) and natural products (e.g., vinca alkyloids and antibiotics). Examples of such anitneoplastic agents include but are not limited to the following:

ADJUNCT ANTINEOPLASIC THERAPY:

Aloprim™ for Injection

Anzemet® Injection

Anzemet® Tablets

Aredia® for Injection

Didronel® I.V. Infusion

Diflucan® Tablets, Injection, and Oral Suspension

Epogen® for Injection

Ergamisol® Tablets

Ethyol® for Injection

Kytril® Injection

Kytril® Tablets

Leucovorin Calcium for Injection

Leucovorin Calcium Tablets

Leukine®

Marinol® Capsules

Mesnex® Injection

Neupogen® for Injection

Procrit® for Injection

Salagen® Tablets

Sandostatin® Injection

Zinecard® for Injection

Zofran® Injection

Zofran® ODT™ Orally Disintegrating Tablets

Zofran® Oral Solution

Zofran® Tablets

Zyloprim® Tablets

ALKYLATING AGENTS:

Myleran® Tablets

Paraplatin® for Injection

Platinol® for Injection

Platinol-AQ® Injection

Thioplex® for Injection

NITROGEN MUSTARDS:

Alkeran® for Injection

Alkeran® Tablets

Cytoxan® for Injection

Cytoxan® Tablets

Ifex® for Injection

Leukeran® Tablets

Mustargen® for Injection

NITROSOUREAS:

BiCNU®

CeeNU®

Gliadel® Wafer

Zanosar® Sterile Powder

ANTIBIOTICS:

Adriamycin® PFS/RDS for Injection

Blenoxane®

Cerubidine® for Injection

Cosmegen® for Injection

DaunoXome®

Doxil® Injection

Doxorubicin Hydrochloride for Injection, USP

Idamycin PFS Injection

Mithracin® for Intravenous Use

Mutamycin® for Injection

Nipent® for Injection

Novantrone® for Injection

Rubex® for Injection

Valstar™ Sterile Solution for Intravesical Instill

5

Lupron® Injection

Zoladex®

PROGESTINS

Depo-Provera® Sterile Aqueous Suspension

Megace® Tablets

IMMUNOMODULATORS

Ergamisol® Tablets

Proleukin® for Injection

MISCELLANEOUS ANTINEOPLASTICS

Camptosar® Injection

Celestone® Soluspan® Suspension

DTIC-Dome®

Elspar® for Injection

Etopophos® for Injection

Etoposide Injection

Gemzar® for Injection

Herceptin® I.V.

Hexalen® Capsules

Hycamtin® for Injection

Hydrea® Capsules

Hydroxyurea Capsules, USP

Intron® A for Injection

Lysodren® Tablets

Matulane® Capsules

Navelbine® Injection

Oncapsar®

Oncovin® Solution Vials and Hyporets

Ontak™ Vials

Proleukin® for Injection

Rituxan™ for Infusion

Rituxan® I.V.

Roferon®-A Injection

Taxol® Injection

Taxotere® for Injection Concentrate

TheraCys®

Tice® BCG Vaccine, USP

Velban® Vials

VePesid® Capsules

VePesid® for Injection

Vesanoid® Capsules

Vumon® for Injection

PHOTOSENSITIZING AGENTS

Photofrin® for Injection

SKIN AND MUCUS MEMBRANE AGENTS

Efudex® Cream

Efudex® Topical Solution

Fluoroplex® Topical Cream

Fluoroplex® Topical Solution

The invention is illustrated by the following Example, which is not intended to be limiting.

Example 1

METHOD: A randomized crossover open label trial was performed. A total of sixty patients, twenty with lung cancer, twenty with gastric cancer and twenty with breast cancer were studied during two complete cycles of chemotherapy. All patients were randomized into two groups. In group 1, patients received chemotherapy with thymosin α_1 in the first cycle, and without thymosin α_1 in the second cycle. While patients in group 2 received chemotherapy without thymosin α_1 in the first cycle, and with thymosin α_1 in the second cycle. The patients were treated as follows:

Twenty lung cancer patients were treated with 100 mg of Etoposide IV on days 1-5 and 40 mg of Cisplatin I.V. on days 1-3 in a 21 day cycle.

Twenty gastric cancer patients were treated with 100 mg of Etoposide IV on days 1-5, 30 mg/m^2 Calcium Leucovorin I.V. on days 1-5 and 500 mg/m^2 5-Fluorouricil (5-FU) I.V. on days 1-5.

Twenty breast cancer patients were treated with 5-Fluorouricil 500 mg/m^2, Adriamycin I.V. 30 mg/m^2 I.V. on day 1 and cyclophosphamide 500 mg/m^2 I.V. on day 1.

A mild anti-emetic consisting of 20 mg metoclopamide, I.M. and 5 mg Dexamethasone I.V. were given to all patients on days 1-5. All subjects on thymosin received six injections of 1.6 mg s.c. $T\alpha_1$ on each of the four days immediately preceding the chemotherapy and on days two and four following chemotherapy. All patients who have completed the two cycles of chemotherapy, then were reallocated into two cohorts, A and B. Cohort A are patients with $T\alpha_1$, and Cohort B are patients without $T\alpha_1$.

ANALYSIS: Quality of life was analyzed using a scored scale for (1) loss of appetite, (2) loss of sleep, (3) fatigue, (4) reduction in daily activity, (5) decline in overall feeling, (6) depression and (7) nausea and vomiting. Maximum total score was 35 points.

RESULTS: A comparison between cycles (with $T\alpha_1$ and without $T\alpha_1$) was performed. The addition of $T\alpha_1$ to chemotherapy cycles significantly increases the quality of life scores compared with cycles without $T\alpha_1$.

Side Effects

Loss of Appetite	4.33 vs. 3.99	p = 0.0001
Loss of Sleep	4.41 vs. 4.10	p = 0.002
Fatigue	4.05 vs. 3.70	p = 0.0001
Reduction in Daily Activity	4.12 vs. 3.84	p = 0.0001
Decline in Overall Feeling	4.32 vs. 3.94	p = 0.0001
Depression	4.01 vs. 3.72	p = 0.003
Nausea and Vomiting	4.29 vs. 3.93	p = 0.001

Nausea and vomiting classified according to WHO criteria:

Group	n	Grade 0	Gr.1	Gr.2	Gr.3	Gr.4	P value
A (with $T\alpha_1$)	54	7/54	33	13	1	0	P<0.0005
B (Without $T\alpha_1$)	53	4/53	19	19	11	0	

CONCLUSION: Adding $T\alpha_1$ to chemotherapy significantly improves patient quality of life.

Throughout the specification, unless the context requires otherwise, the word "comprise" or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

2001255475 29 Nov 2005

The Claims Defining the Invention are as Follows

1. A method of reducing side effects of a chemotherapy agent in a cancer patient, wherein the side effects are selected from the group consisting of loss of appetite, loss of sleep, fatigue, reduction in daily activity, decline in overall feeling, depression, nausea and vomiting and combinations of said side effects, comprising administering to the cancer patient thymosin α_1 ($T\alpha_1$) prior to administration of the chemotherapy agent.

2. The method of claim 1 wherein $T\alpha_1$ is administered prior to administration of at least one chemotherapy agent selected from the group consisting of allopurinol sodium, dolasetron mesylate, pamidronate disodium, etidronate, fluconazole, epoetin alfa, levamisole HCL, amifostine, granisetron HCL, leucovorin calcium, sargramostim, dronabinol, mesna, filgrastim, pilocarpine HCL, octreotide acetate, dexrazoxane, ondansetron HCL, ondansetron, busulfan, carboplatin, cisplatin, thiotepa, melphalan HCL, melphalan, cyclophosphamide, ifosfamide, chlorambucil, mechlorethamine HCL, carmustine, lomustine, polifeprosan 20 with carmustine implant, streptozocin, doxorubicin HCL, bleomycin sulfate, daunirubicin HCL, dactinomycin, daunorucbicin citrate, idarubicin HCL, plimycin, mitomycin, pentostatin, mitoxantrone, valrubicin, cytarabine, fludarabine phosphate, floxuridine, cladribine, methotrexate, mercaptipurine, thioguanine, capecitabine, methyltestosterone, nilutamide, testolactone, bicalutamide, flutamide, anastrozole, toremifene citrate, tamoxifen, estramustine phosphate sodium, ethinyl estradiol, estradiol, esterified estrogens, conjugated estrogens, leuprolide acetate, goserelin acetate, medroxyprogesterone acetate, megestrol acetate, levamisole HCL, aldesleukin, irinotecan HCL, decarbazine, asparaginase, etoposide phosphate, gemcitabine HCL, trastuzumab, altretamine, topotecan HCL, hydroxyurea, interferon alfa-2b, mitotane, procarbazine HCL, vinorelbine tartrate, *E. coli* L-asparaginase, *Erwinia L*-asparaginase, vincristine sulfate, denileukin diftitox, aldesleukin, rituximab, interferon alfa-2a, paclitaxel, docetaxel, BCG live (intravesical), vinblastine sulfate, etoposide, tretinoin, teniposide, porfimer sodium,

fluorouracil, betamethasone sodium phosphate and betamethasone acetate, letrozole, etoposide citrororum factor, folinic acid, calcium leucouorin, 5-fluorouricil, adriamycin, cytoxan, and diamino dichloro platinum, said chemotherapy agent in combination with thymosin α_1 being administered in an amount effective to reduce said side effects of chemotherapy in said patient.

3. The method of claim 1 or 2 wherein said $T\alpha_1$ is also administered subsequent to said chemotherapy agent.

4. The method of claim 1 or 2 wherein said $T\alpha_1$ is administered on each of a plurality of days prior to said chemotherapy agent.

5. The method of claim 1 or 2 wherein a single administration of $T\alpha_1$ is administered one day immediately prior to administration of said chemotherapy agent.

6. The method of claim 1 or 2 wherein a single administration of $T\alpha_1$ is administered on each of two days immediately prior to administration of said chemotherapy agent.

7. The method of claim 1 or 2 wherein a single administration of $T\alpha_1$ is administered on each of three days immediately prior to administration of said chemotherapy agent.

8. The method of claim 1 or 2 wherein a single administration of $T\alpha_1$ is administered on each of four days immediately prior to administration of said chemotherapy agent.

9. The method of claim 3 wherein a single administration of $T\alpha_1$ is administered one day immediately subsequent to administration of said chemotherapy agent.

10. The method of claim 3 wherein a single administration of $T\alpha_1$ is administered on each of two days immediately subsequent to said administration of said chemotherapy agent.

11. The method of claim 3 wherein $T\alpha_1$ is administered on a plurality of days prior to and subsequent to the administration of said chemotherapy agent.

12. The method of claim 3 wherein a single administration of $T\alpha_1$ is administered one day immediately prior to and one day immediately subsequent to administration of said chemotherapy agent.

13. The method of claim 3 wherein a single administration of $T\alpha_1$ is administered on each of two days immediately days prior to and two days immediately subsequent to the administration of said chemotherapy agent.

14. The method of claim 1 or 2 wherein $T\alpha_1$ is administered at a dosage within a range of about .1 – 3.2mg.

15. The method of claim 1 or 2 wherein $T\alpha_1$ is administered at a dosage of about 1.6mg.

16. The method of claim 1 wherein said chemotherapy agent is selected from the group consisting of antineoplastic alkylating agents, antineoplastic antimetabolites, antineoplastic radioactive isotopes, antineoplastic hormones, antineoplastic ureas, antineoplastic vinca alkaloids, antineoplastic antibiotics, and combinations thereof.

17. The method of claim 16 wherein said antineoplastic alkylating agents are nitrogen mustards, said antineoplastic antimetabolites are pyrimidine analogs, said antineoplastic radioactive isotopes are radioactive

phosphorous, radioactive iodine or a combination thereof, and said antineoplastic hormones are estrogens, adrenocorticosteroids, and combinations thereof.

18. The method of claim 1 or 2 wherein said chemotherapy agent is selected from the group consisting of etoposide citrororum factor, folinic acid, calcium leucourin, 5-fluorouricil, adriamycin, cytoxan, diamino dichloro platinum and combinations thereof.

19. A method according to claim 1 substantially as herein before described with reference to the example.

Dated this FIRST day of MARCH 2005.

SciClone Pharmaceuticals, Inc.
Applicant

Wray & Associates
Perth, Western Australia
Patent Attorneys for the Applicant