DESCRIPTION

Title of Invention

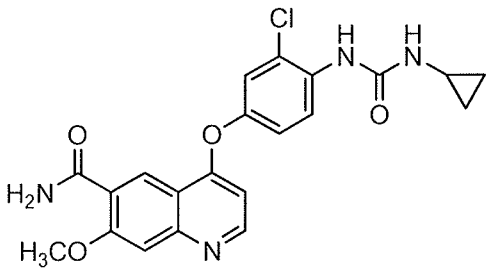
TUMOR THERAPEUTIC AGENT

Technical Field

[0001] The present invention relates to a tumor therapeutic agent used for a combination therapy of lenvatinib, ifosfamide, and etoposide.

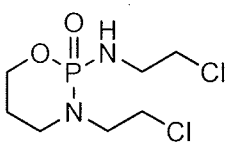
Background Art

[0002]



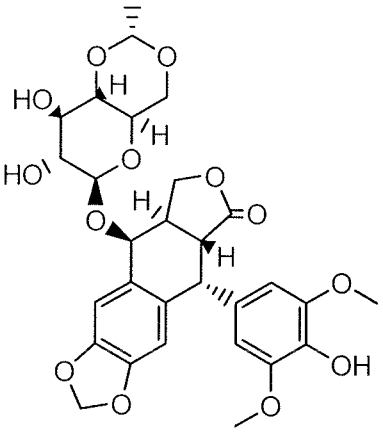
[0003] Lenvatinib has angiogenesis inhibitory effect (Patent Literature 1) and inhibitory effect (Patent Literatures 2 to 5) against tyrosine kinase, which is reported to be involved in the malignant transformation of tumors (Non-Patent Literatures 1 to 5), and lenvatinib is known as a therapeutic agent for various tumors, such as thyroid cancer, lung cancer, melanoma, endometrial cancer, gastric cancer, bladder cancer, renal cancer, glioma, liver cancer, and ovarian cancer.

[0004]



[0005] Ifosfamide is known as a therapeutic agent for many malignant tumors, such as small cell lung cancer, prostate cancer, cervical cancer, and osteosarcoma.

[0006]



[0007] Etoposide is known as a therapeutic agent for malignant tumors, such as small cell lung cancer, malignant lymphoma, and acute leukemia.

[0008] In general, tumor therapeutic agents are often not effective for all patients when they are used alone. Accordingly, attempts have been made so far to improve the treatment rate by using a plurality of tumor therapeutic agents in combination to enhance antitumor effects and reduce adverse effects (Patent Literature 6 and Patent Literature 7).

[0009] The combined administration of ifosfamide and etoposide is used for malignant tumors, such as osteosarcoma and Ewing's sarcoma (Non-Patent Literatures 6 to 8).

Citation List

Patent Literature

[0010]

Patent Literature 1: U.S. Patent Application Publication No. 2004-053908

Patent Literature 2: U.S. Patent Application Publication No. 2004-253205

Patent Literature 3: U.S. Patent Application Publication No. 2010-105031

Patent Literature 4: U.S. Patent Application Publication No. 2009-209580

Patent Literature 5: U.S. Patent Application Publication No. 2009-264464

Patent Literature 6: U.S. Patent Application Publication No. 2011-104161

Patent Literature 7: U.S. Patent Application Publication No. 2004-259834

Non Patent Literature

[0011]

Non-Patent Literature 1: Lasota et al., "Mutations in Exons 9 and 13 of KIT Gene Are Rare Events in Gastrointestinal Stromal Tumors," American Journal of Pathology, vol. 157, pp. 1091-1095, 2000

Non-Patent Literature 2: Berdel et al., "Recombinant Human Stem Cell Factor Stimulates

Growth of a Human Glioblastoma Cell Line Expressing c-kit Protooncogene1," Cancer Research, vol. 52, pp. 3498-3502, 1992

Non-Patent Literature 3: Lennartsson et al., "The stem cell factor receptor/c-Kit as a drug target in cancer," Current Cancer Drug Targets, vol. 6, pp. 65-75, 2006

Non-Patent Literature 4: Turner et al., "Fibroblast growth factor signalling: from development to cancer," Nature Reviews Cancer, vol. 10, pp. 116-129, 2010

Non-Patent Literature 5: Wells et al, "Targeting the RET Pathway in Thyroid Cancer," Clinical Cancer Research, vol. 15, pp. 7119-7123, 2009

Non-Patent Literature 6: The ESMO/European Sarcoma Network Working Group, "Bone sarcomas: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up," Annals of Oncology, vol. 23, supplement 7, vii100-vii109, 2012

Non-Patent Literature 7: Gentet et al., "Ifosfamide and etoposide in childhood osteosarcoma. A phase II study of the French Society of Paediatric Oncology," European Journal of Cancer, vol. 33, pp. 232-237, 1997

Non-Patent Literature 8: Grier et al., "Addition of Ifosfamide and Etoposide to Standard Chemotherapy for Ewing's Sarcoma and Primitive Neuroectodermal Tumor of Bone," The New England Journal of Medicine, vol. 348, pp. 694-701, 2003

Summary of Invention

Technical Problem

[0012] However, the therapeutic effects of the combined use of tumor therapeutic agents ever reported are not sufficient, and development of combination therapy using further new tumor therapeutic agents has been awaited.

Solution to Problem

[0013] In view of the above circumstances, the present inventors conducted extensive research, and consequently found that combined administration of lenvatinib, ifosfamide, and etoposide surprisingly showed antitumor effects more than expected; thus, the present invention has been completed.

[0014] That is, the present invention provides the followings:

[1] A therapeutic agent for a tumor comprising lenvatinib or a pharmacologically acceptable salt thereof, wherein lenvatinib or the pharmacologically acceptable salt thereof is administered in combination with ifosfamide and etoposide or a pharmacologically acceptable salt thereof.

[2] A pharmaceutical composition comprising lenvatinib or a pharmacologically acceptable

salt thereof, wherein lenvatinib or the pharmacologically acceptable salt thereof is administered in combination with ifosfamide and etoposide or a pharmacologically acceptable salt thereof.

[3] A pharmaceutical composition for treating a tumor, comprising lenvatinib or a pharmacologically acceptable salt thereof, wherein lenvatinib or the pharmacologically acceptable salt thereof is administered in combination with ifosfamide and etoposide or a pharmacologically acceptable salt thereof.

[4] A method for treating a tumor, comprising administering lenvatinib or a pharmacologically acceptable salt thereof, ifosfamide, and etoposide or a pharmacologically acceptable salt thereof to a patient in need thereof.

[5] Lenvatinib or a pharmacologically acceptable salt thereof, wherein the lenvatinib or a pharmacologically acceptable salt thereof is administered in combination with ifosfamide and etoposide or a pharmacologically acceptable salt thereof.

[6] Lenvatinib or a pharmacologically acceptable salt thereof for treating a tumor, wherein the lenvatinib or a pharmacologically acceptable salt thereof is administered in combination with ifosfamide and etoposide or a pharmacologically acceptable salt thereof.

[7] A pharmaceutical composition comprising lenvatinib or a pharmacologically acceptable salt thereof for treating a tumor, wherein lenvatinib or the pharmacologically acceptable salt thereof is administered in combination with ifosfamide and etoposide or a pharmacologically acceptable salt thereof.

[8] Use of lenvatinib or a pharmacologically acceptable salt thereof for the manufacture of a pharmaceutical composition for treating a tumor, wherein lenvatinib or the pharmacologically acceptable salt thereof is administered in combination with ifosfamide and etoposide or a pharmacologically acceptable salt thereof.

[9] Use of lenvatinib or a pharmacologically acceptable salt thereof for treating a tumor, wherein lenvatinib or the pharmacologically acceptable salt thereof is administered in combination with ifosfamide and etoposide or a pharmacologically acceptable salt thereof.

[10] A kit comprising a formulation comprising lenvatinib or a pharmacologically acceptable salt thereof, a formulation comprising ifosfamide, and a formulation comprising etoposide or a pharmacologically acceptable salt thereof.

[11] The kit according to [10], wherein the kit is a kit for treating a tumor.

[12] A therapeutic agent for a tumor comprising lenvatinib or a pharmacologically acceptable salt thereof, ifosfamide, and etoposide or a pharmacologically acceptable salt thereof.

[13] A pharmaceutical composition comprising lenvatinib or a pharmacologically acceptable salt thereof, ifosfamide, and etoposide or a pharmacologically acceptable salt thereof.

[14] A pharmaceutical composition for treating a tumor, the pharmaceutical composition comprising lenvatinib or a pharmacologically acceptable salt thereof, ifosfamide, and etoposide or a pharmacologically acceptable salt thereof.

[15] Lenvatinib or a pharmacologically acceptable salt thereof, ifosfamide, and etoposide or a pharmacologically acceptable salt thereof for treating a tumor.

[16] Use of lenvatinib or a pharmacologically acceptable salt thereof, ifosfamide, and etoposide for the manufacture of a therapeutic agent for a tumor.

[17] The above therapeutic agent for treating a tumor or pharmaceutical composition, further comprising an excipient.

[18] The above therapeutic agent for treating tumor, pharmaceutical composition, treatment method, use, compound, or kit, wherein the lenvatinib or a pharmacologically acceptable salt thereof is lenvatinib mesylate.

[19] The above therapeutic agent for treating a tumor, pharmaceutical composition, treatment method, use, compound, or kit, wherein the etoposide or a pharmacologically acceptable salt thereof is etoposide phosphate.

[20] The above therapeutic agent for treating tumor, pharmaceutical composition, treatment method, use, compound, or kit, wherein the lenvatinib or a pharmacologically acceptable salt thereof, ifosfamide, and etoposide or a pharmacologically acceptable salt thereof are administered simultaneously, separately, continuously, or at time intervals.

[21] The above therapeutic agent for treating a tumor, pharmaceutical composition, treatment method, use, compound, or kit, wherein the tumor is osteosarcoma, Ewing's sarcoma, rhabdomyosarcoma, neuroblastoma, retinoblastoma, hepatoblastoma, or nephroblastoma.

[22] The therapeutic agent for treating a tumor, pharmaceutical composition, treatment method, use, compound, or kit according to [21], wherein the tumor is osteosarcoma.

[23] The therapeutic agent for treating a tumor, pharmaceutical composition, treatment method, use, compound, or kit according to [22], wherein the osteosarcoma is relapsed or refractory.

Advantageous Effects of Invention

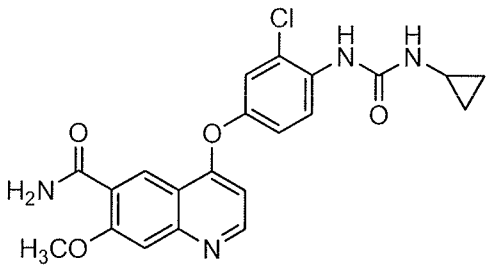
[0015] The present invention provides a therapeutic agent for a tumor used for a combination therapy of lenvatinib, ifosfamide, and etoposide. This therapeutic agent for a tumor exhibits unexpected antitumor effects for patients in need thereof.

Description of Embodiments

[0016] Embodiments of the present invention are described below. The following embodiments are only examples for describing the present invention, and it is not intended to limit the present invention only to these embodiments. The present invention can be carried out in various forms without departing from the subject matter of the present invention.

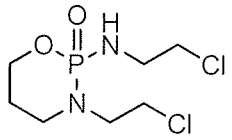
Note that the documents, publications, patent publications, and other patent literatures cited in the present description are incorporated herein by reference. The present specification includes the contents of U.S. Provisional Application No. 62/207,546 (filed on August 20, 2015), which is the basis for claiming the priority of the present application.

[0017] Lenvatinib refers to 4-(3-chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide, and the structural formula thereof is shown in the following formula:



Lenvatinib or a pharmacologically acceptable salt thereof can be produced by the method described in Patent Literature 1. An example of pharmacologically acceptable salts of lenvatinib is lenvatinib mesylate. Lenvatinib mesylate is also referred to as E7080.

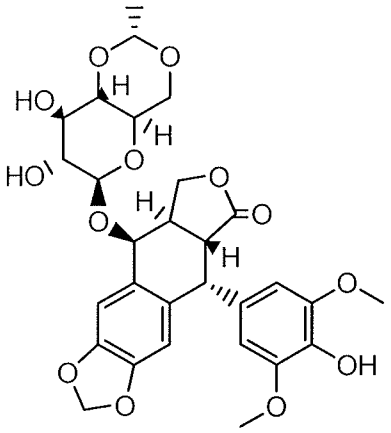
[0018] Ifosfamide refers to 3-(2-chloroethyl)-2-[(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine-2-oxide, and the structural formula thereof is shown in the following formula:



Ifosfamide can be produced by a known method, and can be produced, for example, by the method described in U.S. Patent No. 3732340. Moreover, ifosfamide can be obtained by purchasing Ifex (registered trademark) from Bristol-Myers Squibb, or by purchasing Ifomide (registered trademark) from Shionogi & Co., Ltd.

[0019] Etoposide refers to (5R,5aR,8aR,9S)-9-{[4,6-O-(1R)-ethylidene-β-D-glucopyranosyl]oxy}-5-(4-hydroxy-3,5-dimethoxyphenyl)-5,8,8a,9-

tetrahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-6(5aH)-one, and the structural formula thereof is shown in the following formula:



Etoposide can be produced by a known method, and can be produced, for example, by the method described in U.S. Patent No. 3524844. Moreover, etoposide can be obtained by purchasing VePesid (registered trademark) from Bristol-Myers Squibb. An example of pharmacologically acceptable salts of etoposide is etoposide phosphate.

[0020] Although the "pharmacologically acceptable salt" is not limited to a specific type of salt, examples thereof include salts with inorganic acids, salts with organic acids, salts with inorganic bases, salts with organic bases, and salts with acidic or basic amino acids.

[0021] Examples of salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, and phosphoric acid. Examples of salts with organic acids include salts with acetic acid, succinic acid, fumaric acid, maleic acid, tartaric acid, citric acid, lactic acid, stearic acid, benzoic acid, methanesulfonic acid (mesylic acid), ethanesulfonic acid, and p-toluenesulfonic acid.

[0022] Examples of salts with inorganic bases include alkali metal salts, such as sodium salt and potassium salt; alkaline earth metal salts, such as a calcium salt and a magnesium salt; an aluminum salt and an ammonium salt. Examples of salts with organic bases include salts with diethylamine, diethanolamine, meglumine, and N,N-dibenzylethylenediamine.

[0023] Examples of salts with acidic amino acids include salts with aspartic acid and glutamic acid. Examples of salts with basic amino acids include salts with arginine, lysine, and ornithine.

[0024] Examples of pharmacologically acceptable salts of lenvatinib include salts with organic acids, and one embodiment thereof is methanesulfonate (mesylate).

[0025] Examples of pharmacologically acceptable salts of etoposide include salts with

inorganic acids, and one embodiment thereof is phosphate.

[0026] When solvates and optical isomers of the lenvatinib, ifosfamide, or etoposide of the present invention are present, these solvates and optical isomers are included. Examples of solvates include hydrate and anhydrate. Examples of solvents include water, alcohols (e.g., methanol, ethanol, and n-propanol), and dimethylformamide.

[0027] Moreover, the lenvatinib, ifosfamide, or etoposide of the present invention may be crystalline or amorphous. When polymorphic crystals are present, a single crystal form or a mixture of any of these crystal forms may be used.

[0028] The dose of lenvatinib or a pharmacologically acceptable salt thereof can be suitably selected, depending on the degree of symptoms, the development of adverse effects, the age, sex, body weight, and sensitivity difference of the patient, administration route, administration period, administration interval, the type of pharmaceutical formulation, etc.

[0029] The dose of lenvatinib or a pharmacologically acceptable salt thereof is not particularly limited, but is generally, when orally administered to an adult (body weight: 60 kg) or an child, 0.1 to 500 mg, 0.5 to 300 mg, or 1 to 100 mg, per day, or is 0.1 to 500 mg/m^2 (body surface area, hereinafter the same), 0.5 to 300 mg/m^2, or 1.0 to 100 mg/m^2, per day. This dose can be generally administered once a day, or two to three times a day. If the patient has undergone excessive toxicity, it is necessary to reduce the dose. The dose and dosage schedule may be changed when one or more additional chemotherapeutic agents are used, in addition to the combination therapy of the present invention. The dosage schedule can be determined by the physician who is treating the specific patient.

[0030] Ifosfamide can be administered according to known clinical practice. The dose and dosage schedule can be changed according to the specific disease symptoms and the total symptoms of the patient. The dose can be suitably reduced, depending on age, sex, symptoms, development of adverse effects, etc.

[0031] The dose of ifosfamide is not particularly limited, but is generally, when administered to an adult (body weight: 60 kg) or an child orally, intravenously, or by intravenous drip infusion, 0.01 to 100 g/m^2, 0.05 to 30 g/m^2, or 0.1 to 10 g/m^2, per day, or 0.01 to 100 g, 0.05 to 30 g, or 0.1 to 10 g per day. One embodiment of the dose of ifosfamide is about 1.5 to 3 g/m^2 per day. This dose can be generally administered for first 3 to 5 days of one cycle consisting of 3 to 4 weeks. Ifosfamide can be repeatedly administered to the patient by repeating this cycle. In one embodiment, about 3 g/m^2 per day of ifosfamide is administered from Day 1 to Day 3 of one cycle consisting of 21 days,

and this cycle is suitably repeated. If the patient has undergone excessive toxicity, it is necessary to reduce the dose. The dose and dosage schedule may be changed when one or more additional chemotherapeutic agents are used. The dosage schedule can be determined by the physician who is treating the specific patient.

[0032] Etoposide or a pharmacologically acceptable salt thereof can be administered according to known clinical practice. The dose and dosage schedule can be changed according to the specific disease symptoms and the total symptoms of the patient. The dose can be suitably reduced, depending on age, sex, symptoms, development of adverse effects, etc.

[0033] The dose of etoposide or a pharmacologically acceptable salt thereof is not particularly limited, but is generally, when administered to an adult (body weight: 60 kg) or an child orally, intravenously, or by intravenous drip infusion, 1.0 to 5000 mg/m^2, 5.0 to 3000 mg/m^2, or 10 to 1000 mg/m^2, per day. One embodiment of the dose of etoposide or a pharmacologically acceptable salt thereof is about 60 to about 120 mg/m^2 as etoposide per day. This dose can be generally administered for first 3 to 5 days of one cycle consisting of 3 to 4 weeks. Etoposide or a pharmacologically acceptable salt thereof can be repeatedly administered to the patient by repeating this cycle. If the patient has undergone excessive toxicity, it is necessary to reduce the dose. In one embodiment, about 100 mg/m^2, as etoposide per day, of etoposide or a pharmacologically acceptable salt thereof is administered from Day 1 to Day 3 of one cycle consisting of 21 days, and this cycle is suitably repeated. The dose and dosage schedule may be changed when one or more additional chemotherapeutic agents are used. The dosage schedule can be determined by the physician who is treating the specific patient.

[0034] The dose of lenvatinib, ifosfamide, or etoposide in the combined administration of the present invention can generally be set equal to or lower than the dose when they are administered alone. The specific dose, administration route, administration frequency, administration cycle, etc., are suitably determined, in consideration of the age, sex, and symptoms of the patient, the development of adverse effects, etc.

[0035] The dosage form of lenvatinib, ifosfamide, and etoposide in the present invention is not particularly limited, and it is only necessary to administer lenvatinib, ifosfamide, and etoposide in combination when administered. For example, lenvatinib, ifosfamide, and etoposide are each administered to the patient simultaneously, separately, continuously, or at time intervals. Here, the term "simultaneously" means that the ingredients are each

administered in the same period or exactly at the same time, or administered through the same route. The term "separately" means that the ingredients are each administered in different intervals or with different frequencies, or administered through different routes. The term "continuously" means that the ingredients are each administered through the same or different routes in an arbitrary order within a predetermined period. The term "at time intervals" means that the ingredients are each administered through the same or different routes at intervals for the respective ingredients. In the combined administration of lenvatinib and ifosfamide, when lenvatinib is administered during one cycle of administration of ifosfamide described above or during a period in which this cycle is repeated, it is determined that lenvatinib and ifosfamide are administered in combination. In the combined administration of lenvatinib and etoposide or a pharmacologically acceptable salt thereof, when lenvatinib is administered during one cycle of administration of etoposide or a pharmacologically acceptable salt thereof described above or during a period in which this cycle is repeated, it is determined that lenvatinib and etoposide or a pharmacologically acceptable salt thereof are administered in combination. In one dosage form in the combined administration of the present invention, lenvatinib is orally administered, and ifosfamide and etoposide are administered intravenously or by intravenous infusion. Moreover, the combined administration of the present invention may be conducted simultaneously, separately, continuously, or at time intervals, together with the administration of a therapeutic agent for a tumor other than lenvatinib, ifosfamide, and etoposide.

[0036] The therapeutic agent for a tumor of the present invention can be formulated, for example, by the method described in the 16th Revised Japanese Pharmacopoeia (JP), United States Pharmacopeia (USP), or European Pharmacopoeia (EP).

[0037] The tumor therapeutic agent of the present invention can be orally administered in the form of a solid formulation, such as a tablet, a granule, a fine granule, a powder, or a capsule; or a liquid formulation, a jelly, or a syrup.

[0038] Moreover, the tumor therapeutic agent of the present invention may be parenterally administered in the form of an injection, a suppository, an ointment, a cataplasm, or the like.

[0039] When an oral solid formulation is prepared, an excipient, and further a binder, a disintegrator, a lubricant, a coloring agent, a flavoring agent, a surfactant, etc., can be added, if necessary, as additives to lenvatinib or a pharmacologically acceptable salt thereof, ifosfamide, or etoposide or a pharmacologically acceptable salt thereof, thereby forming a

tablet, a granule, a subtle granule, a powder, a capsule, etc., by a conventional method. The above additives can be suitably combined for formulation. Furthermore, these tablets, granules, etc., may be coated, if necessary.

[0040] When an injection is prepared, a pH adjuster, a buffer, a suspending agent, a solubilizing agent, a stabilizer, an isotonizing agent, a preservative, etc., may be added, if necessary, to lenvatinib or a pharmacologically acceptable salt thereof, ifosfamide, or etoposide or a pharmacologically acceptable salt thereof, thereby forming an intravenous, subcutaneous, or intramuscular injection, or an intravenous infusion by a conventional method. In this case, the injections can be formed, if necessary, as lyophilized products by a conventional method.

[0041] Tumors targeted by the present invention are not particularly limited, and examples of tumors include brain tumors (including hypophysial adenoma and glioma), head and neck cancer, cervical cancer, jaw cancer, maxillary cancer, submandibular gland cancer, oral cancer (including tongue cancer, mouth floor cancer, gingival cancer, buccal mucosa cancer, and hard palate cancer), salivary gland cancer, sublingual gland cancer, parotid gland cancer, nasal cavity cancer, paranasal sinus cancer (including maxillary sinus cancer, frontal sinus cancer, ethmoid sinus cancer, and sphenoid sinus cancer), laryngeal cancer (including supraglottic cancer, glottic cancer, and subglottic cancer), esophageal cancer, lung cancer (including bronchogenic cancer, non-small cell lung cancer (including lung adenocarcinoma, squamous cell carcinoma, and large cell lung carcinoma), small cell lung cancer (including oat cell (lymphoid) and intermediate cell types), and mixed small cell/large cell lung cancer), breast cancer, pancreatic cancer (including pancreatic duct cancer), gastric cancer (including scirrhous gastric cancer and undifferentiated gastric cancer (including undifferentiated adenocarcinoma, signet-ring cell carcinoma, and mucinous carcinoma)), biliary tract cancer (including bile duct cancer and gallbladder cancer), small intestinal or duodenal cancer, colorectal cancer (including colon cancer, rectal cancer, cecal cancer, sigmoid colon cancer, ascending colon cancer, transverse colon cancer, and descending colon cancer), bladder cancer, renal cancer (including renal cell cancer), hepatic cancer (including liver cell cancer and intrahepatic bile duct cancer), prostate cancer, uterine cancer (including cervical cancer and endometrial cancer), ovarian cancer, thyroid cancer, pharyngeal cancer (including nasopharyngeal cancer, oropharyngeal cancer, and hypopharyngeal cancer), sarcomas (e.g., osteosarcoma, Ewing's sarcoma, rhabdomyosarcoma, chondrosarcoma, Kaposi's sarcoma, angiosarcoma, fibrosarcoma, etc.), neuroblastoma, retinoblastoma, hepatoblastoma,

nephroblastoma, malignant lymphomas (including Hodgkin's lymphoma and non-Hodgkin's lymphoma), leukemia (including, for example, chronic myelocytic leukemia (CML), acute myelocytic leukemia (AML), chronic lymphocytic leukemia (CLL) and acute lymphocytic leukemia (ALL), lymphoma, multiple myeloma (MM), myelodysplastic syndrome, etc.), skin cancer (including basal cell cancer, squamous cell cancer, malignant melanoma, mycosis fungoides, Sezary's syndrome, solar keratosis, Bowen's disease, and Paget's disease) and melanoma; and mixed tumors thereof. In one embodiment of the present invention, the target tumor is osteosarcoma, Ewing's sarcoma, rhabdomyosarcoma, neuroblastoma, retinoblastoma, hepatoblastoma, or nephroblastoma. In another embodiment of the present invention, the target tumor is osteosarcoma. Moreover, the tumors targeted by the present invention include relapsed or refractory tumors.

Examples

[0042] Specific examples of the present invention are provided below; however, the present invention is not limited thereto.

[0043] [Example 1] Tumor growth inhibitory activity of the combined use of lenvatinib, ifosfamide, and etoposide against human osteosarcoma cell line (143B) subcutaneous transplantation models

Using 6 NOD SCID mice (NOD.CB17-Prkdc^{scid}/J, female mice, Charles River Laboratories Japan, Inc.) in each group, antitumor effects were evaluated when lenvatinib alone, a combination of two agents, i.e., ifosfamide and etoposide, or a combination of three agents, i.e., lenvatinib, ifosfamide, and etoposide, was administered. Cells of osteosarcoma cell line 143B (ATCC CRL-8303) derived from human were suspended at a concentration of 1×10^7 cells/mL, and 0.1 mL of the suspension was subcutaneously transplanted to the right flank of each mouse.

The longest diameter and short axis of the tumor were measured with an electronic digital caliper (Digimatic (tread mark) Caliper, Mitutoyo Corporation) 9 days after transplantation. The mice were divided into groups so that the average value of the tumor volume of each group was almost equal (Day 1). The tumor volume was calculated according to the following equation:

Tumor volume = longest diameter (mm) x short axis (mm) x short axis (mm) / 2

[0044] Lenvatinib mesylate was dissolved in purified water to a concentration of 0.3 mg/mL. Ifosfamide (Sigma Aldrich) was dissolved in a physiological saline solution to a concentration of 25 mg/mL. Moreover, an etoposide injection (20 mg/mL solution, Bristol-

Myers Squibb) was diluted with a physiological saline solution to a concentration of 0.8 mg/mL.

Purified water and a physiological saline solution were administered to a control group. A lenvatinib solution and a physiological saline solution were administered to a lenvatinib group. An ifosfamide solution, an etoposide solution, and purified water were administered to an ifosfamide + etoposide combination group. A lenvatinib solution, an ifosfamide solution, and an etoposide solution were administered to a 3-agent combination group.

The administration dose of lenvatinib mesylate was 3 mg/kg, and 10 mL/kg was orally administered once a day for 7 days (Day 1 to Day 7). The administration dose of ifosfamide was 250 mg/kg, and 10 mL/kg was intraperitoneally administered once (Day 1). The administration dose of etoposide was 8 mg/kg, and 10 mL/kg was intraperitoneally administered once a day for 3 days (Day 2 to Day 4). Purified water was orally administered in an amount of 10 mL/kg once a day for 7 days (Day 1 to Day 7). A physiological saline solution was intraperitoneally administered in an amount of 10 mL/kg once a day for 4 days (Day 1 to Day 4).

[0045] The tumor volume of each mouse was measured 8 days (Day 8) after the start of administration. The results are shown in Table 1. It was clarified that the combined use of the three agents, i.e., lenvatinib, ifosfamide, and etoposide, had excellent antitumor effects against the human osteosarcoma cell-line (143B) subcutaneous transplantation models.

[0046] [Table 1]

Group	Average tumor volume (Day 8) mm^3
Control group	785.4
Lenvatinib group	438.6
Ifosfamide + etoposide combination group	495.9
3-agent combination group	184.7

[0047] [Example 2] Tumor growth inhibitory activity of the combined use of lenvatinib, ifosfamide, and etoposide against human osteosarcoma cell line (G-292 clone A141B1) subcutaneous transplantation models

Using 6 NOD SCID mice (NOD.CB17-Prkdc^{scid}/J, female mice, Charles River Laboratories Japan, Inc.) in each group, antitumor effects were evaluated when lenvatinib alone, a combination of two agents, i.e., ifosfamide and etoposide, or a combination of three agents, i.e., lenvatinib, ifosfamide, and etoposide, was administered. Cells of osteosarcoma

cell line G-292 clone A141B1 (JCRB Cell Bank, IFO50107) derived from human were suspended at a concentration of $1x10^8$ cells/mL, and 0.1 mL of the suspension was subcutaneously transplanted to the right flank of each mouse.

The longest diameter and short axis of the tumor were measured with an electronic digital caliper (Digimatic (tread mark) Caliper, Mitutoyo Corporation) 29 days after transplantation. The mice were divided into groups so that the average value of the tumor volume of each group was almost equal (Day 1). The tumor volume was calculated according to the following equation:

Tumor volume = longest diameter (mm) x short axis (mm) x short axis (mm) / 2

[0048] Lenvatinib mesylate was dissolved in purified water to a concentration of 0.3 mg/mL. Ifosfamide (Sigma Aldrich) was dissolved in a physiological saline solution to a concentration of 25 mg/mL. Moreover, an etoposide injection (20 mg/mL solution, Bristol-Myers Squibb) was diluted with a physiological saline solution to a concentration of 0.8 mg/mL.

Purified water and a physiological saline solution were administered to a control group. A lenvatinib solution and a physiological saline solution were administered to a lenvatinib group. An ifosfamide solution, an etoposide solution, and purified water were administered to an ifosfamide + etoposide combination group. A lenvatinib solution, an ifosfamide solution, and an etoposide solution were administered to a 3-agent combination group.

The administration dose of lenvatinib mesylate was 3 mg/kg, and 10 mL/kg was orally administered once a day for 7 days (Day 1 to Day 7). The administration dose of ifosfamide was 250 mg/kg, and 10 mL/kg was intraperitoneally administered once (Day 1). The administration dose of etoposide was 8 mg/kg, and 10 mL/kg was intraperitoneally administered once a day for 3 days (Day 2 to Day 4). Purified water was orally administered in an amount of 10 mL/kg once a day for 7 days (Day 1 to Day 7). A physiological saline solution was intraperitoneally administered in an amount of 10 mL/kg once a day for 4 days (Day 1 to Day 4).

[0049] The tumor volume of each mouse was measured 8 days (Day 8) after the start of administration. The results are shown in Table 2. It was clarified that the combined use of the three agents, i.e., lenvatinib, ifosfamide, and etoposide, had excellent antitumor effects against the human osteosarcoma cell line (G-292 clone A141B1) subcutaneous transplantation models.

[0050] [Table 2]

Group	Average tumor volume (Day 8) mm^3
Control group	362.5
Lenvatinib group	267.9
Ifosfamide + etoposide combination group	286.0
3-agent combination group	208.9

[0051] [Example 3] Tumor growth inhibitory activity of the combined use of lenvatinib, ifosfamide, and etoposide against human osteosarcoma cell line (HOS) subcutaneous transplantation models

Using 6 NOD SCID mice (NOD.CB17-Prkdc^{scid}/J, female mice, Charles River Laboratories Japan, Inc.) in each group, antitumor effects were evaluated when lenvatinib alone, a combination of two agents, i.e., ifosfamide and etoposide, or a combination of three agents, i.e., lenvatinib, ifosfamide, and etoposide, was administered. Cells of osteosarcoma cell line HOS (Human Science Research Resources Bank, IFO50106) derived from human were suspended at a concentration of 1 x 10^8 cells/mL, and 0.1 mL of the suspension was subcutaneously transplanted to the right of each mouse.

The longest diameter and short axis of the tumor were measured with an electronic digital caliper (Digimatic (tread mark) Caliper, Mitutoyo Corporation) 18 days after transplantation. The mice were divided into groups so that the average value of the tumor volume of each group was almost equal (Day 1). The tumor volume was calculated according to the following equation:

Tumor volume = longest diameter (mm) x short axis (mm) x short axis (mm) / 2

[0052] Lenvatinib mesylate was dissolved in purified water to a concentration of 0.3 mg/mL. Ifosfamide (Sigma Aldrich) was dissolved in a physiological saline solution to a concentration of 25 mg/mL. Moreover, an etoposide injection (20 mg/mL solution, Bristol-Myers Squibb) was diluted with a physiological saline solution to a concentration of 0.8 mg/mL.

Purified water and a physiological saline solution were administered to a control group. A lenvatinib solution and a physiological saline solution were administered to a lenvatinib group. An ifosfamide solution, an etoposide solution, and purified water were administered to an ifosfamide + etoposide combination group. A lenvatinib solution, an ifosfamide solution, and an etoposide solution were administered to a 3-agent combination group.

The administration dose of lenvatinib mesylate was 3 mg/kg, and 10 mL/kg was orally administered once a day for 7 days (Day 1 to Day 7). The administration dose of ifosfamide was 250 mg/kg, and 10 mL/kg was intraperitoneally administered once (Day 1). The administration dose of etoposide was 8 mg/kg, and 10 mL/kg was intraperitoneally administered once a day for 3 days (Day 2 to Day 4). Purified water was orally administered in an amount of 10 mL/kg once a day for 7 days (Day 1 to Day 7). A physiological saline solution was intraperitoneally administered in an amount of 10 mL/kg once a day for 4 days (Day 1 to Day 4).

[0053] The tumor volume of each mouse was measured 8 days (Day 8) after the start of administration. The results are shown in Table 3. It was clarified that the combined use of the three agents, i.e., lenvatinib, ifosfamide, and etoposide, had excellent antitumor effects against the human osteosarcoma cell line (HOS) subcutaneous transplantation models.

[0054] [Table 3]

Group	Average tumor volume (Day 8) mm^3
Control group	468.6
Lenvatinib group	352.2
Ifosfamide + etoposide combination group	433.0
3-agent combination group	252.1

[0055] [Example 4] Phase 1/2 clinical trial of lenvatinib for children and adolescents with relapsed or refractory solid malignant tumors

The present clinical trial is a phase 1/2 clinical trial for evaluating the safety, tolerance, and efficacy of lenvatinib in children and adolescents who have relapsed or refractory solid malignant tumors.

[0056] The present clinical trial consists of 5 cohorts (Cohorts 1, 2A, 2B, 3A, and 3B), and a primary object of each cohort is as follows:

To determine the recommended dose (RD) of lenvatinib in children and adolescents who have relapsed or refractory solid malignant tumors using the time-to-event continual reassessment method (TiTE-CRM) [Cohort 1]. In the present clinical trial, the RD is defined as a dose at which the incidence of dose limiting toxicity (DLT) is closest to the target level, i.e., 20%.

To evaluate the objective response rate (ORR) of lenvatinib in children and adolescents who have 131 iodine-refractory differentiated thyroid cancer (DTC) [Cohort 2A]. The objective response rate is defined as complete response (CR) + partial response

(PR), based on the Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

To evaluate the progression-free survival (PFS) at 4 months after administration of lenvatinib alone in children and adolescents who have relapsed or refractory osteosarcoma [Cohort 2B]. The progression-free survival (PFS) at 4 months is the rate of participants who survive for 4 months after the start of administration of lenvatinib alone and whose disease does not progress (based on RECIST 1.1).

To set the RD of lenvatinib when used in combination with ifosfamide and etoposide in children and adolescents who have relapsed or refractory solid malignant tumors [Cohort 3A]. The dose of a combination of lenvatinib, ifosfamide, and etoposide at which DLT occurs in one or less of the 6 cases is taken into consideration as the RD of combination therapy.

To evaluate the progression-free survival (PFS) at 4 months after administration of a combination of lenvatinib, ifosfamide, and etoposide in children and adolescents who have relapsed or refractory osteosarcoma [Cohort 3B]. The progression-free survival (PFS) at 4 months is the rate of participants who survive for 4 months after the start of combined use of lenvatinib, ifosfamide, and etoposide and whose disease does not progress (based on RECIST 1.1).

[0057] Secondary objects of the present clinical trial are as follows:

Best overall response (BOR) [all cohorts]

Objective response rate (ORR) [Cohorts 1, 2B, 3A, and 3B]

Duration of response (DOR) [all cohorts]

Disease control rate (DCR) [all cohorts]

Clinical benefit rate (CBR) [all cohorts]

Time to progression (TTP) [all cohorts]

Overall survival (OS) [all cohorts]

The number of participants who experienced adverse events (AEs)/serious adverse events (SAEs) as the safety and tolerance evaluation

Plasma concentration of lenvatinib: area under the drug concentration-time curve (AUC) [all cohorts]

Pharmacodynamics (PD) biomarkers: VEGFR and FGFR [all cohorts]

[0058] The present clinical trial consists of 5 cohorts.

In Cohort 1 (single agent dose setting), in order to set the recommended dose (RD) of lenvatinib in children and adolescents who have relapsed or refractory solid malignant

tumors, the dose is gradually increased using the time-to-event continual reassessment method (TiTE-CRM). Once the RD is set, Cohorts 2A, 2B, and 3A are started in parallel.

In Cohort 2 (single agent expansion cohort), the efficacy of lenvatinib at the RD in children and adolescents who have 131 iodine-refractory differentiated thyroid cancer [Cohort 2A] or relapsed or refractory osteosarcoma [Cohort 2B] is evaluated.

In Cohort 3A (combined-use dose setting), the RD of lenvatinib when used in combination with ifosfamide and etoposide in participants who have relapsed or refractory osteosarcoma is determined.

In Cohort 3B (combined-use expansion cohort), the efficacy of the combined use of lenvatinib, ifosfamide, and etoposide at the RD obtained in Cohort 3A in participants who have relapsed or refractory osteosarcoma is evaluated. Participants with osteosarcoma who are registered in Cohort 1 or 2B and whose disease have progressed after administration of lenvatinib become candidates for participants of Cohort 3B, as with participants with relapsed or refractory osteosarcoma to which lenvatinib has not been administered.

[0059] In the present clinical trial, lenvatinib is provided as a hard capsule containing 1.225 mg, 4.9 mg, or 12.25 mg of lenvatinib mesylate (1 mg, 4 mg, or 10 mg as lenvatinib). For children who cannot swallow capsules, the lenvatinib capsule is dissolved in water.

[0060] In Cohort 1, lenvatinib is orally administered once a day at a starting dose of 11 mg/m^2 from Day 1 to Day 28 of a 28-day cycle. The dose can be reduced to 9 mg/m^2, or increased to 14 and 17 mg/m^2.

In Cohort 2A, lenvatinib is orally administered once a day at the RD determined in Cohort 1 from Day 1 to Day 28 of a 28-day cycle.

In Cohort 2B, lenvatinib is orally administered once a day at the RD determined in Cohort 1 from Day 1 to Day 28 of a 28-day cycle.

In Cohort 3A, lenvatinib is orally administered once a day at a dose (starting dose) 20% lower than the RD determined in Cohort 1 from Day 1 to Day 21 of a 21-day cycle. Ifosfamide is administered at a dose of 3000 mg/m^2/day (starting dose) from Day 1 to Day 3 of a 21-day cycle for 5 cycles in total. Etoposide is administered at a dose of 100 mg/m^2/day (starting dose) from Day 1 to Day 3 of a 21-day cycle for 5 cycles in total.

In Cohort 3B, lenvatinib is orally administered once a day at the RD determined in Cohort 3A from Day 1 to Day 21 of a 21-day cycle. Ifosfamide is administered at the dose set in Cohort 3A from Day 1 to Day 3 of a 21-day cycle for 5 cycles in total. Etoposide is administered at the dose set in Cohort 3A from Day 1 to Day 3 of a 21-day cycle for 5 cycles

in total.

[0061] From the results of the present clinical study, the efficacy, safety, and tolerance of lenvatinib alone for 131 iodine-refractory differentiated thyroid cancer, those of lenvatinib alone for relapsed or refractory osteosarcoma, and those of the 3-agent combined use of lenvatinib, ifosfamide, and etoposide for relapsed or refractory osteosarcoma can be confirmed.

CLAIMS

1. Use of lenvatinib or a pharmacologically acceptable salt thereof for the manufacture of a pharmaceutical composition for treating a tumor, wherein lenvatinib or the pharmacologically acceptable salt thereof is to be administered in combination with ifosfamide and etoposide or a pharmacologically acceptable salt thereof.

2. The use according to claim 1, wherein the lenvatinib or a pharmacologically acceptable salt thereof is lenvatinib mesylate.

3. The use according to any one of claims 1 to 2, wherein the etoposide or a pharmacologically acceptable salt thereof is etoposide phosphate.

4. The use according to any one of claims 1 to 3, wherein the lenvatinib or a pharmacologically acceptable salt thereof, ifosfamide, and etoposide or a pharmacologically acceptable salt thereof are to be administered simultaneously, separately, continuously, or at time intervals.

5. The use according to any one of claims 1 to 4, wherein the tumor is osteosarcoma, Ewing's sarcoma, rhabdomyosarcoma, neuroblastoma, retinoblastoma, hepatoblastoma, or nephroblastoma.

6. The use according to claim 5, wherein the tumor is osteosarcoma.

7. The use according to claim 6, wherein the osteosarcoma is relapsed or refractory.