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CA 3035334 C 2022/05/10

(11)(21) 3 035 334

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2017/08/30
(87) Date publication PCT/PCT Publication Date: 2018/03/08
(45) Date de délivrance/Issue Date: 2022/05/10
(85) Entrée phase nationale/National Entry: 2019/02/27
(86) N° demande PCT/PCT Application No.: JP 2017/031074
(87) N° publication PCT/PCT Publication No.: 2018/043530
(30) Priorité/Priority: 2016/08/31 (JP2016-169167)

(51) Cl.Int./Int.Cl. *A61K 31/7068* (2006.01), *A61K 31/337* (2006.01), *A61K 47/42* (2017.01), *A61K 9/14* (2006.01), *A61P 35/00* (2006.01), *A61P 43/00* (2006.01)

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(54) Titre : COMBINAISON D'ACLITAXELAND 1-(2-DEOXY-2-FLUORO-4-THIO-BETA-D- ARABINOFURANOSYLE)-CYTOSINE COMME AGENT ANTITUMORAL

(54) Title: COMBINATION OF PACLITAXELAND 1-(2-DEOXY-2-FLUORO-4-THIO-BETA-D-ARABINOFURANOSYL)-CYTOSINE AS ANTI-TUMOR AGENT

(57) Abrégé/Abstract:
An object of the present invention is to provide an anti-tumor agent and an anti-turnor kit which have superior anti-tumor effect as compared with a therapy with gerncitabine, paclitaxel or a combination thereof; as well as an anti-tumor effect enhancer. According to the present invention, provided is an anti-tumor agent including paclitaxel or a salt thereof and 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine or a salt or prodrug thereof.

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Certificat de correction

Certificate of Correction

Canadian Patent No. 3,035,334
Granted: 10 May 2022 (10-05-2022)

Les corrections suivantes sont faites en raison de l'article 109 des *Règles sur les brevets* et le brevet doit être lu tel que corrigé.

The following corrections are made pursuant to section 109 of the *Patent Rules* and the patent should read as corrected.

In the Patent Grant:

The attached page 1 should be read in place of page 1 in the description.

13 June 2022 (13-06-2022)

Date

Canada

COMBINATION OF PACLITAXEL AND 1-(2-DEOXY-2-FLUORO-4-THIO-BETA-D-ARABINOFURANOSYL)-CYTOSINE AS ANTI-TUMOR AGENT

Field of the Invention

[0001] The present invention relates to an anti-tumor agent, an anti-tumor effect enhancer, and an anti-tumor kit.

Description of the Related Art

[0002] It is known that 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine (hereinafter, sometimes referred to as "Compound A") has excellent anti-tumor activity and is therefore useful as an anti-tumor agent (Patent Documents 1 and 2). It is also known that Compound A has potent anti-tumor activity also in the case of oral administration thereof to mice (Non-Patent Documents 1 and 2). A salt of Compound A and a method for producing the same are also known (Patent Documents 2 to 4).

[0003] In chemotherapy of malignant tumors, taxane-based anti-tumor agents such as paclitaxel and nab-paclitaxel are also used as useful drugs. However, it is known that the response rate to tumor with a taxane-based anti-tumor agent alone is as low as 10% to 25%, and the survival period of cancer patients is short (survival period of 12 to 15 months) (Non-Patent Document 3).

[0004] In a clinical setting, a multidrug combination therapy has been carried out for the purpose of compensating for differences in susceptibility of each anti-tumor agent to tumor and of enhancing the drug efficacy, and a medicine combining paclitaxel and other drugs is also known (Patent Document 5). For example, combination use of gemcitabine and nab-paclitaxel to pancreatic cancer patients has a response rate of 23% and a median survival period of 8.5 months (Non-Patent Document 4), which cannot be said that the therapeutic effect is sufficiently high.

Prior Art Documents

Patent Documents

[0005]

Patent Document 1: WO1997/038001A

Patent Document 2: WO2013/146833A

Patent Document 3: WO2011/074484A

Patent Document 4: WO2014/027658A

Patent Document 5: WO2013/100014A

Date Reçue/Date Received 2022-05-13

ABSTRACT

An object of the present invention is to provide an anti-tumor agent and an anti-tumor kit which have superior anti-tumor effect as compared with a therapy with gemcitabine, paclitaxel or a combination thereof; as well as an anti-tumor effect enhancer. According to the present invention, provided is an anti-tumor agent including paclitaxel or a salt thereof and 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine or a salt or prodrug thereof.

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[0001] The present invention relates to an anti-tumor agent, an anti-tumor effect enhancer, and an anti-tumor kit.

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[0003] In chemotherapy of malignant tumors, taxane-based anti-tumor agents such as paclitaxel and nab-paclitaxel are also used as useful drugs. However, it is known that the response rate to tumor with a taxane-based anti-tumor agent alone is as low as 10% to 25%, and the survival period of cancer patients is short (survival period of 12 to 15 months) (Non-Patent Document 3).

[0004] In a clinical setting, a multidrug combination therapy has been carried out for the purpose of compensating for differences in susceptibility of each anti-tumor agent to tumor and of enhancing the drug efficacy, and a medicine combining paclitaxel and other drugs is also known (Patent Document 5). For example, combination use of gemcitabine and nab-paclitaxel to pancreatic cancer patients has a response rate of 23% and a median survival period of 8.5 months (Non-Patent Document 4), which cannot be said that the therapeutic effect is sufficiently high.

Prior Art Documents

Patent Documents

[0005]

Patent Document 1: WO1997/038001A

Patent Document 2: WO2013/146833A

Patent Document 3: WO2011/074484A

Patent Document 4: WO2014/027658A

Patent Document 5: WO2013/100014A

Date Reçue/Date Received 2021-01-25

Non-Patent Documents

[0006]

Non-Patent Document 1: Cancer Letters, 1999, Vol. 144, pp. 177 to 182

Non-Patent Document 2: Oncology Reports, 2002, Vol. 9, pp. 1319 to 1322

Non-Patent Document 3: Journal of Clinical Oncology, 2005, Vol. 23, pp. 7794 to 7803

Non-Patent Document 4: New England Journal of Medicine, 2013, Vol. 369, pp. 1691 to 1703

SUMMARY OF THE INVENTION

[0007] In recent years, a combination therapy has been widely carried out rather than administering an anti-tumor agent alone. However, it is completely unknown whether any anti-tumor effect will be enhanced or the effect will be offset in the case where any anti-tumor agents are used in combination.

An object of the present invention is to provide an anti-tumor agent and an anti-tumor kit which have superior anti-tumor effect as compared with a therapy with gemcitabine, paclitaxel or a combination thereof; as well as an anti-tumor effect enhancer.

[0008] In view of the above, the present inventors have studied combination use of various drugs, and as a result, have found that combination use of paclitaxel and Compound A exhibits significant anti-tumor effect. The present invention has been completed based on these findings.

That is, the present invention provides the following.

(1) An anti-tumor agent comprising paclitaxel or a salt thereof and 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine or a salt or prodrug thereof.

(2) The anti-tumor agent according to (1), in which the amount of the 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine or the salt or prodrug thereof used is 0.01 to 100-fold molar amount of the paclitaxel or the salt thereof.

(3) The anti-tumor agent according to (1) or (2), in which the anti-tumor agent is for pancreatic cancer.

(4) The anti-tumor agent according to any one of (1) to (3), in which the paclitaxel is a nanoparticle containing paclitaxel and albumin.

(5) The anti-tumor agent according to any one of (1) to (4), in which the paclitaxel is nab-paclitaxel.

(6) An anti-tumor effect enhancer, comprising 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine or a salt or prodrug thereof to be

used in combination with paclitaxel or a salt thereof.

(7) An anti-tumor kit comprising a preparation containing paclitaxel or a salt thereof and a preparation containing 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine or a salt or prodrug thereof.

(8) An anti-tumor agent comprising 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine or a salt or prodrug thereof to be used in combination with paclitaxel or a salt thereof.

(6-1) The anti-tumor effect enhancer according to (6), in which the paclitaxel is a nanoparticle containing paclitaxel and albumin.

(6-2) The anti-tumor effect enhancer according to (6) or (6-1), in which the paclitaxel is nab-paclitaxel.

(7-1) The anti-tumor kit according to (7), in which the paclitaxel is a nanoparticle containing paclitaxel and albumin.

(7-2) The anti-tumor kit according to (7) or (7-1), in which the paclitaxel is nab-paclitaxel.

(8-1) The anti-tumor agent according to (8), in which the paclitaxel is a nanoparticle containing paclitaxel and albumin.

(8-2) The anti-tumor agent according to (8) or (8-1), in which the paclitaxel is nab-paclitaxel.

(9) A method for use of paclitaxel or a salt thereof and 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine or a salt or prodrug thereof in the treatment of a tumor, preferably the treatment of pancreatic cancer, comprising a step of administering a therapeutically effective dose thereof to a subject (a mammal including a human) in need of such treatment.

(10) A method for treating a tumor, characterized in that a therapeutically effective dose of 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine or a salt or prodrug thereof in the case of being used in combination therapy and a therapeutically effective dose of paclitaxel or a salt thereof in the case of being used in combination therapy are administered in combination to a subject.

(11) A method for treating a tumor, characterized in that a therapeutically effective dose of 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine or a salt or prodrug thereof in the case of being used in combination therapy and a therapeutically effective dose of paclitaxel or a salt thereof in the case of being used in combination therapy are administered to

a subject simultaneously, separately, sequentially, or at intervals.

(12) Use of 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine or a salt or prodrug thereof for the production of an anti-tumor agent in combination with paclitaxel or a salt thereof.

(13) Use of 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine or a salt or prodrug thereof for an anti-tumor agent in combination with paclitaxel or a salt thereof.

(14) 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine or a salt or prodrug thereof for treating a tumor by administration thereof as a single dosage form with paclitaxel or a salt thereof or as a dosage form separate from paclitaxel or a salt thereof.

[0009] Compound A or a salt or prodrug thereof exhibits significant anti-tumor effect in the case of being used in combination with paclitaxel. That is, the anti-tumor agent and anti-tumor kit of the present invention have superior tumor regression and tumor growth inhibitory effects as compared with gemcitabine alone, paclitaxel alone, or a combination of gemcitabine and paclitaxel. The anti-tumor effect enhancer of the present invention can be administered in combination with paclitaxel or a salt thereof to enhance anti-tumor effect.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] Fig. 1 is a graph showing the transition of tumor volume in a human pancreatic cancer cell line Capan-1 subcutaneously implanted tumor-bearing model mouse.

Fig. 2 is a graph showing the transition of body weight in a human pancreatic cancer cell line Capan-1 subcutaneously implanted tumor-bearing model mouse.

Fig. 3 is a graph showing a combinational effect of inhibiting tumor growth in a human pancreatic cancer cell line Capan-1 subcutaneously implanted tumor-bearing model mouse.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0011] In the present invention, the numerical value represented by "%" is based on the mass unless otherwise stated. In addition, the range expressed by "to" includes the values at both ends unless otherwise stated.

The term "subject" is a mammal such as a human, a mouse, a monkey, or a livestock in need of prevention or treatment thereof, preferably a human in need of prevention or treatment thereof.

The term "preventing" refers to inhibition of disease onset, reduction of disease onset risk, or delay of disease onset.

The term "treating" refers to improvement of, or inhibition (maintenance or delay) of

progression of a target disease or condition.

The term "treatment" refers to preventing, treating, or the like of a variety of diseases.

The term "tumor" refers to a benign tumor or a malignant tumor.

The term "benign tumor" refers to a tumor in which a tumor cell and a sequence thereof take a form close to a normal cell from which such a tumor cell is derived, and which is free of invasiveness or metastatic properties.

The term "malignant tumor" refers to a tumor in which the morphology and sequence of a tumor cell are different from a normal cell from which such a tumor cell is derived, and which exhibits invasiveness or metastatic properties.

Hereinafter, the present invention will be described in detail.

The present invention relates to an anti-tumor agent including paclitaxel or a pharmaceutically acceptable salt thereof (hereinafter, sometimes referred to as a "salt thereof") and 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine (Compound A) or a salt or prodrug thereof. Further, the present invention also relates to an anti-tumor agent including paclitaxel or a salt thereof in combination with Compound A or a salt or prodrug thereof.

[0012] First, Compound A or a salt or prodrug thereof will be described.

The salt may be, for example, a pharmaceutically acceptable salt and specific examples thereof include a mineral acid salt, an organic carboxylate, and a sulfonate. Preferred examples of the salt include a mineral acid salt and a sulfonate.

[0013] Examples of the mineral acid salt include hydrochloride, hydrobromide, hydroiodide, nitrate, phosphate, and sulfate, among which hydrochloride, hydroiodide, nitrate, or sulfate is preferable, and hydrochloride is more preferable. Examples of the organic carboxylate include formate, acetate, citrate, oxalate, fumarate, maleate, succinate, malate, tartrate, aspartate, trichloroacetate, and trifluoroacetate. Examples of the sulfonate include methanesulfonate, benzenesulfonate, p-toluenesulfonate, mesitylenesulfonate, and naphthalenesulfonate, among which methanesulfonate is preferable.

[0014] The salt of Compound A may be an anhydride, a hydrate, or a solvate. In the case where the term "salt" is simply used in the present specification, it may be in the form of anhydride, hydrate, or solvate. As for the term "anhydride" used in the present specification, it refers to the salt in a state where it is not a hydrate or a solvate, unless otherwise stated. Even though it is a substance which originally does not form a hydrate or a solvate, the salt of Compound A which does not have crystallization water, hydration water and an interacting solvent is also included in the "anhydride" referred to in the present invention. Anhydride

may also be referred to as "anhydrate". In the case where the salt of Compound A is a hydrate, the molecular number of hydration water is not particularly limited, and the hydrate may be a monohydrate, a dihydrate, or the like. Examples of the solvate include methanol solvate, ethanol solvate, propanol solvate, and 2-propanol solvate.

[0015] Particularly preferred specific examples of Compound A are as follows:

methanesulfonate of 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine;

hydrochloride of 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine;

½ sulfate of 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine;

nitrate of 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine; and

hydroiodide of 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine; as well as anhydrides of the foregoing salts.

[0016] The prodrug refers to a compound or a salt thereof which is converted into a compound exhibiting a desired pharmacological activity, following cleavage of a functional group functioning as a prodrug by a reaction with an enzyme, gastric juice, or the like in the body after administration thereof.

Examples of groups forming a prodrug include the groups described in Stella VJ et al., Prodrugs: Challenges and Rewards. Parts 1 and 2, 2007, American Association of Pharmaceutical Scientists.

[0017] The prodrug of Compound A refers to a compound or a salt thereof which converts into Compound A or a phosphate compound thereof by a reaction with an enzyme, gastric juice, or the like under physiological conditions in vivo.

As to the prodrug of Compound A, the description of WO2016/068341A can be referred to.

More specifically, for example, a thionucleoside derivative represented by General Formula [1] or a salt thereof described in WO2016/068341A can be used herein, and a preferred range thereof is also the same as that described in WO2016/068341A.

[0018] In the present invention, Compound A or a salt or prodrug thereof may be used alone or in combination of two or more thereof.

[0019] Next, a method for producing Compound A or a salt or prodrug thereof will be described. Compound A can be produced, for example, by the method described in WO1997/038001A or Journal of Organic Chemistry, 1999, Vol. 64, pp. 7912 to 7920. The salt of Compound A or a hydrate or solvate thereof can be produced, for example, by the method described in WO2014/027658A. The prodrug of Compound A can be produced, for

Date Reçue/Date Received 2020-07-06

example, by the method described in WO2016/068341A.

Compound A or a salt or prodrug thereof according to the present invention can be used as an anti-tumor agent or as an active ingredient of a pharmaceutical composition.

[0020] In the present invention, paclitaxel or a salt thereof may be used alone or in combination of two or more thereof. Paclitaxel or a salt thereof may be a composition containing them, in addition to paclitaxel or a salt thereof.

The salt may be, for example, a pharmaceutically acceptable salt and specific examples thereof include salts in commonly known basic groups such as amino group, and salts in commonly known acidic groups such as hydroxyl group and carboxyl group.

Examples of salts in basic groups include salts with mineral acids such as hydrochloric acid, hydrobromic acid, nitric acid, and sulfuric acid; salts with organic carboxylic acids such as formic acid, acetic acid, citric acid, oxalic acid, fumaric acid, maleic acid, succinic acid, malic acid, tartaric acid, aspartic acid, trichloroacetic acid, and trifluoroacetic acid; and salts with sulfonic acids such as methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, mesitylene sulfonic acid, and naphthalene sulfonic acid.

Examples of salts in acidic groups include salts with alkali metals such as sodium and potassium; salts with alkaline earth metals such as calcium and magnesium; ammonium salts; and salts with nitrogen-containing organic bases such as trimethylamine, triethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, diethylamine, dicyclohexylamine, procaine, dibenzylamine, N-benzyl-β-phenethylamine, 1-ephenamine, and N,N'-dibenzylethylenediamine.

Examples of the composition containing paclitaxel or a salt thereof include a nanoparticle containing paclitaxel and albumin (preferably human serum albumin) (albumin-bound paclitaxel injection suspension of nanoparticle preparation encapsulating paclitaxel with albumin (nab-paclitaxel, trade name "Abraxane™")); a polymeric micelle (NK 105) in which paclitaxel is encapsulated in a block copolymer of polyethylene glycol and polyaspartic acid; a prodrug in which fatty acid docosahexaenoic acid (DHA) is conjugated to paclitaxel (trade name Taxoprexin™); a prodrug in which polyglutamic acid is conjugated to paclitaxel (trade name "Opaxio™"); and a prodrug in which a monoclonal antibody targeting a tumor cell is conjugated to paclitaxel.

Paclitaxel is preferably a nanoparticle containing paclitaxel and albumin and more preferably nab-paclitaxel.

Date Reçue/Date Received 2020-07-06

[0021] Compound A is an anti-tumor agent having an excellent DNA synthesis inhibitory effect. In the case where Compound A is used in combination with paclitaxel, it is expected that such a combination will have an effect of enhancing the anti-tumor effect of paclitaxel without showing significant exacerbation of toxicity.

[0022] (Anti-tumor agent)

According to the present invention, provided are

an anti-tumor agent including paclitaxel or a salt thereof and 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine or a salt or prodrug thereof; and

an anti-tumor agent including 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine or a salt or prodrug thereof to be used in combination with paclitaxel or a salt thereof.

Typically, the anti-tumor agent of the embodiment of the present invention may contain additives such as an excipient, a binder, a lubricant, a disintegrant, a coloring agent, a flavoring agent, an emulsifier, a surfactant, a solubilizing agent, a suspending agent, a tonicity agent, a buffering agent, a preservative, an antioxidant, a stabilizer, and an absorption promoter, which have been used in the formulation.

[0023] The anti-tumor agent of the embodiment of the present invention including paclitaxel or a salt thereof and Compound A or a salt or prodrug thereof may be a single dosage form containing paclitaxel or a salt thereof and Compound A or a salt or prodrug thereof, or may be a binary dosage form containing paclitaxel or a salt thereof and Compound A or a salt or prodrug thereof. Preferably, the anti-tumor agent of the embodiment of the present invention is a binary dosage form in which paclitaxel or a salt thereof and Compound A or a salt or prodrug thereof are separately formulated.

In the case where paclitaxel or a salt thereof and Compound A or a salt or prodrug thereof are used as separate preparations, individual preparations can be administered to a subject simultaneously, separately, sequentially, or at intervals. In addition, the means for administering a composition containing paclitaxel and the means for administering a composition containing Compound A may be the same or different (for example, oral administration and injection).

[0024] The route of administration of the anti-tumor agent of the embodiment of the present invention may be, for example, a method such as intravenous, intraarterial, rectal, intraperitoneal, intramuscular, intratumoral or intravesical injection, oral administration, transdermal administration and/or through suppositories.

Parenteral administration is preferred as the route of administration. For example, intravenous injection (intravenous infusion) such as drip infusion, intramuscular injection, intraperitoneal injection, subcutaneous injection, intraocular injection and/or intrathecal injection can be mentioned as the parenteral administration. The method of administration includes administration by syringe or drip infusion.

[0025] The dose or blending amount of paclitaxel or a salt thereof and Compound A or a salt or prodrug thereof contained in the anti-tumor agent of the embodiment of the present invention is not particularly limited as long as it exerts an effect of enhancing the anti-tumor effect, but Compound A or a salt or prodrug thereof may be used in an amount of 0.01 to 100 mol, preferably 0.1 to 50 mol, and more preferably 1 to 40 mol per 1 mol of paclitaxel.

[0026] With respect to the dosage and administration frequency of paclitaxel or a salt thereof, for example, for an adult, for example a dose of 1 to 1000 mg/m^2/day can be administered once or in several divided portions by oral or parenteral administration (for example, injection, drip infusion, or rectal administration).

With respect to the dosage and administration frequency of Compound A or a salt or prodrug thereof, a dose of 1 to 2000 mg/m^2/day can be administered once or in several divided portions. However, it is not limited to these doses and administration frequencies.

[0027] Examples of dosage forms of the anti-tumor agent of the embodiment of the present invention include a tablet, a capsule, a powder, a syrup, a granule, a pill, a suspension, an emulsion, a solution, a suppository, an eye drop, a nasal drop, an ear drop, a patch, an ointment, and an injection, among which an injection is preferred. Each of these dosage forms can be produced by a formulation method conventionally known to those skilled in the art.

[0028] The anti-tumor agent of the embodiment of the present invention can be effectively used for the treatment of various types of tumors including, for example, melanoma, liver cancer, glioma, neuroblastoma, sarcoma, and tumors of the lung, colon, breast, bladder, ovary, testis, prostate, cervix, pancreas, stomach, small intestine and other organs. The anti-tumor agent of the embodiment of the present invention is preferably an antineoplastic agent, can be used as an anticancer agent, and is particularly effective for the treatment of pancreatic cancer.

[0029] (Anti-tumor kit)

The anti-tumor kit of the embodiment of the present invention is a kit including a combination of (a) paclitaxel or a salt thereof and (b) Compound A or a salt or prodrug thereof.

In the kit, (a) paclitaxel or a salt thereof and (b) Compound A or a salt or prodrug thereof can each be in various known preparation forms, and depending on the preparation

form, (a) and (b) are contained in various commonly used containers.

Further, in the kit, (a) paclitaxel or a salt thereof and (b) Compound A or a salt or prodrug thereof may be contained in separate containers or may be mixed and stored in the same container. It is preferred that (a) paclitaxel or a salt thereof and (b) Compound A or a salt or prodrug thereof are contained in separate containers.

[0030] (Anti-tumor effect enhancer)

The anti-tumor effect enhancer of the embodiment of the present invention is an anti-tumor agent including 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine or a salt or prodrug thereof to be used in combination with paclitaxel or a salt thereof.

Typically, the anti-tumor effect enhancer of the embodiment of the present invention may contain additives such as an excipient, a binder, a lubricant, a disintegrant, a coloring agent, a flavoring agent, an emulsifier, a surfactant, a solubilizing agent, a suspending agent, a tonicity agent, a buffering agent, a preservative, an antioxidant, a stabilizer, and an absorption promoter, which have been used in the formulation.

[0031] The anti-tumor effect enhancer of the embodiment of the present invention can be administered to a subject simultaneously with, separately from, sequentially with, or at intervals with paclitaxel or a salt thereof.

[0032] Parenteral administration is preferred as the route of administration of the anti-tumor effect enhancer of the embodiment of the present invention. For example, intravenous injection (intravenous infusion) such as drip infusion, intramuscular injection, intraperitoneal injection, subcutaneous injection, intraocular injection and/or intrathecal injection can be mentioned as the parenteral administration. The method of administration includes administration by syringe or drip infusion.

[0033] The dose or blending amount of Compound A or a salt or prodrug thereof contained in the anti-tumor effect enhancer of the embodiment of the present invention is not particularly limited as long as it exerts an effect of enhancing the anti-tumor effect, but Compound A or a salt or prodrug thereof may be used in an amount of 0.01 to 100 mol, preferably 0.1 to 50 mol, and more preferably 1 to 40 mol per 1 mol of paclitaxel.

[0034] With respect to the dosage and administration frequency of Compound A or a salt or prodrug thereof contained in the anti-tumor effect enhancer of the embodiment of the present invention, a dose of 1 to 2000 mg/m^2/day can be administered once or in several divided portions. However, it is not limited to these doses and administration frequencies.

[0035] The anti-tumor effect enhancer of the embodiment of the present invention can be

effectively used for the treatment of various types of tumors including, for example, melanoma, liver cancer, glioma, neuroblastoma, sarcoma, and tumors of the lung, colon, breast, bladder, ovary, testis, prostate, cervix, pancreas, stomach, small intestine and other organs. The anti-tumor effect enhancer of the embodiment of the present invention is preferably an antineoplastic effect enhancer, and is particularly effective for the treatment of pancreatic cancer.

[0036] The present invention provides a method for use of paclitaxel or a salt thereof and 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine or a salt or prodrug thereof in the treatment of a tumor, preferably the treatment of pancreatic cancer, including a step of administering a therapeutically effective dose thereof to a subject (a mammal including a human) in need of such treatment.

[0037] Further, the present invention provides a method for treating a tumor, characterized in that a therapeutically effective dose of 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine or a salt or prodrug thereof in the case of being used in combination therapy and a therapeutically effective dose of paclitaxel or a salt thereof in the case of being used in combination therapy are administered in combination to a subject.

[0038] Further, the present invention provides a method for treating a tumor, characterized in that a therapeutically effective dose of 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine or a salt or prodrug thereof in the case of being used in combination therapy and a therapeutically effective dose of paclitaxel or a salt thereof in the case of being used in combination therapy are administered to a subject simultaneously, separately, sequentially, or at intervals.

[0039] Use of 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine or a salt or prodrug thereof can be made for the production of an anti-tumor agent in combination with paclitaxel or a salt thereof.

[0040] Use of 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine or a salt or prodrug thereof can be made for an anti-tumor agent in combination with paclitaxel or a salt thereof.

[0041] According to the present invention, it is possible to obtain 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine or a salt or prodrug thereof for treating a tumor by administration thereof as a single dosage form with paclitaxel or a salt thereof or as a dosage form separate from paclitaxel or a salt thereof.

[0042] Further, according to the present invention, it is possible to obtain an anti-tumor agent

including 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine or a salt or prodrug thereof, which is used in combination with paclitaxel or a salt thereof.

Examples

[0043] Hereinafter, the present invention will be described in more detail with reference to Examples and Test Examples, but the present invention is not limited to these Examples and the like. In addition, the maximum tolerated dose (MTD) indicated by paper reports and the like was used for setting doses of various anti-tumor agents whose anti-tumor effect is enhanced as shown in the following Test Examples.

[0044] (Example 1)

Methanesulfonate of 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine (Compound A) was synthesized by the method described in WO2013/146833A.

[0045] (Test Example 1)

Combinational effect test in Capan-1 subcutaneously implanted tumor-bearing model mouse

Gemcitabine (hereinafter, also referred to as Gem), Abraxane (hereinafter, also referred to as Abx), and methanesulfonate of Compound A were used as test substances.

Gemcitabine was prepared by dissolving gemcitabine hydrochloride (manufactured by Teva Pharmaceutical Industries Limited) in physiological saline. Abraxane was prepared by dissolving Abraxane (manufactured by Celgene Corporation) in physiological saline.

Capan-1 cell, a human pancreatic cancer cell line, was subcutaneously injected into the posterior flank of 5 to 6-week old female BALB/cA Jcl-nu mice. After tumor implantation, the major diameter (mm) and minor diameter (mm) of the tumor were measured, and the tumor volume (TV) was calculated. Mice were assigned to each group so that the average TV of each group was equal, and the day on which this grouping (n = 8) was carried out was taken as Day 1.

The test liquid in Abraxane alone group was prepared to be 30 mg/kg/day as the administration dose. In addition, the test liquid in Compound A alone group was prepared to be 480 mg/kg/day. Compound A was administered from the mouse tail vein a total of three times from Day 1 once a week, and Abraxane was similarly administered from the mouse tail vein a total of three times from Day 1 once a week. In the combined administration group, Compound A was administered at 480 mg/kg/day and Abraxane was administered at 30 mg/kg/day.

As a comparative experiment, gemcitabine was used as a control. The test liquid of

gemcitabine alone group was prepared to be 240 mg/kg/day. Gemcitabine was administered from the mouse tail vein a total of three times from Day 1 once a week. In the combined administration group, gemcitabine was administered at 240 mg/kg/day and Abraxane was administered at 30 mg/kg/day.

In this test, doses of Compound A and gemcitabine were set using MTD of each drug. Abraxane was used at the maximum dose usable in combination with each drug. An anti-tumor agent exhibits that the dose exhibiting the maximum drug efficacy is very close to the dose expressing toxicity, and the anti-tumor agent is generally evaluated in the vicinity of MTD in order to evaluate the maximum anti-tumor effect possessed by the drug in an animal model. In this test example, the MTD and the maximum effect dose are almost synonymous.

[0046] As an index of anti-tumor effect, TV at Day 33 was measured in each drug administration group. According to the following equation, a relative tumor volume (RTV) with respect to Day 1 and T/C (%) were calculated to evaluate the anti-tumor effect. Evaluation judgment of combinational effect was made as having a combinational effect in the case where the average RTV value of the combined administration group was statistically significantly (Welch's IUT, over all maximum $p<0.05$) smaller than the average RTV value of each individual administration group. The results are shown in Table 1 and Fig. 1. In the table, * indicates that a statistically significant difference was observed in the control group and Gem or Compound A alone group.

TV (mm^3) = (major diameter × minor diameter^2)/2

RTV = (TV at Day 33)/(TV at Day 1)

T/C (%) = [(average RTV value of test liquid administered group)/(average RTV value of control group)] × 100

[0047] [Table 1]

Group name	Dose (mg/kg/day)	RTV (mean±standard deviation)	T/C (%)	vs. control	vs. alone
Control	0	4.01±0.21	100	-	-
Abx	30	2.03±1.11	50.6	*	-
Gem	240	2.74±0.41	68.3	*	-
Abx+Gem	240+30	1.11±0.48	27.7	*	*
Compound A	480	1.29±0.59	32.2	*	-
Abx+Compound A	480+30	0.21±0.12	5.2	*	*

*: statistically significant

[0048] Compound A significantly enhanced the anti-tumor effect of Abraxane. At 480

mg/kg/day, which is a high dose (maximum effect dose) in nude mice, combination use thereof induced significant reduction in the size of the tumor. The effect was thought to be larger than that of the existing drug gemcitabine. A more detailed explanation will be given later.

[0049] Also, body weight (BW) was measured over time as an index of toxicity and an average %body weight change (BWC (%)) up to Day 33 relative to Day 1 was calculated by the following equation (n: weight measurement day, last measurement day corresponds to Day 33 which is the final evaluation day). The results are shown in Fig. 2.

BWC (%) = [(BW at Day n) - (BW at Day 1)]/(BW at Day 1)×100

No exacerbation of body weight loss was observed in combined administration.

[0050] On the combinational effect of the present invention, the results of evaluation using a combination index (CI) which is a quantitative index of the combinational effect are shown. The CI can be calculated by the following equation according to Cancer Research, 2010, Vol. 70, pp. 440 to 446.

That is, in the case where the drugs to be used in combination are drugs 1 and 2,

CI = (T/C at the time of combination use)÷100/{[(T/C of drug 1)÷100]×[(T/C of drug 2)÷100]}

CI = 1: additive effect

CI > 1: antagonistic effect

CI < 1: synergistic effect

The CI in the case where Abraxane and gemcitabine were used in combination was 0.80, and the CI in the case where Abraxane and Compound A were used in combination was 0.32. Since CI < 1, a synergistic effect by combination use is observed, and the synergistic effect of Compound A can be said to be more significant than that of the existing drug gemcitabine.

[0051] In addition, on the combinational effect of the present invention, the results of evaluation using a tumor growth inhibitory effect (growth of control (GC)) are shown. For the evaluation method, the same method as in B of Fig. 5 of Molecular Cancer Therapeutics, 2013, Vol. 12, pp. 2585 to 2696 was used.

As described in the above document, the GC can be calculated by the following equation.

[1] In the case where RTV > 1

GC (%) = [(corresponding drug RTV-1)/(control RTV-1)]×100

[2] In the case where RTV ≤ 1

GC (%) = (corresponding drug RTV-1)×100

Combinational effect was estimated from the drug efficacy with Abraxane and Compound A or gemcitabine alone by the following calculation equation. The results are shown in Fig. 3 and Table 2.

The estimated combination use GC (%) = [GC (%) of Abraxane×drug alone GC (%)]÷100

[0052] For example, in this test example, from Table 1, GC (%) of Abraxane alone is

[(2.03-1)/(4.01-1)]×100=34.2 (%) since RTV > 1,

GC (%) of gemcitabine is [(2.74-1)/(4.01-1)]×100=57.8 (%) since RTV > 1.

Therefore, the estimated combination use GC (%) is (34.2×57.8)÷100=19.8 (%).

On the other hand, the actual GC (%) of the combination use of Abraxane and gemcitabine is [(1.11-1)/(4.01-1)]×100=3.7 (%) from RTV > 1.

As a result, since the estimated combination use GC (%) is 19.8 (%), whereas the actual combination use GC (%) is 3.7 (%), it is thought that there is a significant combinational effect exceeding the assumed combinational effect.

In the case where the same calculation is carried out also for Compound A, GC (%) of Compound A is [(1.29-1)/(4.01-1)]×100=9.6 (%) since RTV > 1 for single drug.

Therefore, the estimated combination use GC (%) is (34.2×9.6)÷100=3.3 (%)

The actual GC (%) is (0.21-1)×100=-79.0 (%) from RTV ≤ 1. The solid arrow in Fig. 3 indicates the combinational effect of gemcitabine and the dotted arrow indicates the combinational effect of Compound A.

As a result, also in Compound A, the estimated combination use GC (%) is 3.3 (%), whereas the actual combination use GC (%) is -79.0 (%), from which it is thought that there is a significant combinational effect exceeding the assumed combinational effect. It can be said that the degree of combinational effect is more prominent than the existing drug gemcitabine.

[0053] [Table 2]

	Dose (mg/kg/day)	RTV (mean±standard deviation)	GC (%)	Estimated combination use GC (%)
Control	0	4.01±0.21	-	-
Abx	30	2.03±1.11	34.2	-
Gem	240	2.74±0.41	57.8	-
Abx+Gem	240+30	1.11±0.48	3.7	19.8
Compound A	480	1.29±0.59	9.6	-

Abx+Compound A	480+30	0.21±0.12	-79.0	3.3

[0054] The present invention is useful as an anti-tumor agent and an anti-tumor kit which exhibit significant anti-tumor effect, as well as an anti-tumor effect enhancer.

WHAT IS CLAIMED IS:

1. An anti-tumor agent comprising:

paclitaxel or a salt thereof; and

1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine or a salt thereof,

wherein the anti-tumor agent is for pancreatic cancer.

2. The anti-tumor agent according to claim 1, wherein the amount of the 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine or the salt thereof used is 0.01 to 100-fold molar amount of the paclitaxel or the salt thereof.

3. The anti-tumor agent according to claim 1 or 2, wherein the paclitaxel is a nanoparticle containing paclitaxel and albumin.

4. The anti-tumor agent according to any one of claims 1 to 3, wherein the paclitaxel is nab-paclitaxel.

5. An anti-tumor effect enhancer comprising:

1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine or a salt thereof in combination with paclitaxel or a salt thereof for use in the treatment of pancreatic cancer.

6. An anti-tumor kit comprising:

a preparation containing paclitaxel or a salt thereof, and an additive; and

a preparation containing 1-(2-deoxy-2-fluoro-4-thio-β-D-arabinofuranosyl)cytosine or a salt thereof, and an additive;

wherein the anti-tumor kit is for pancreatic cancer.

Date Reçue/Date Received 2021-07-21

FIG. 1

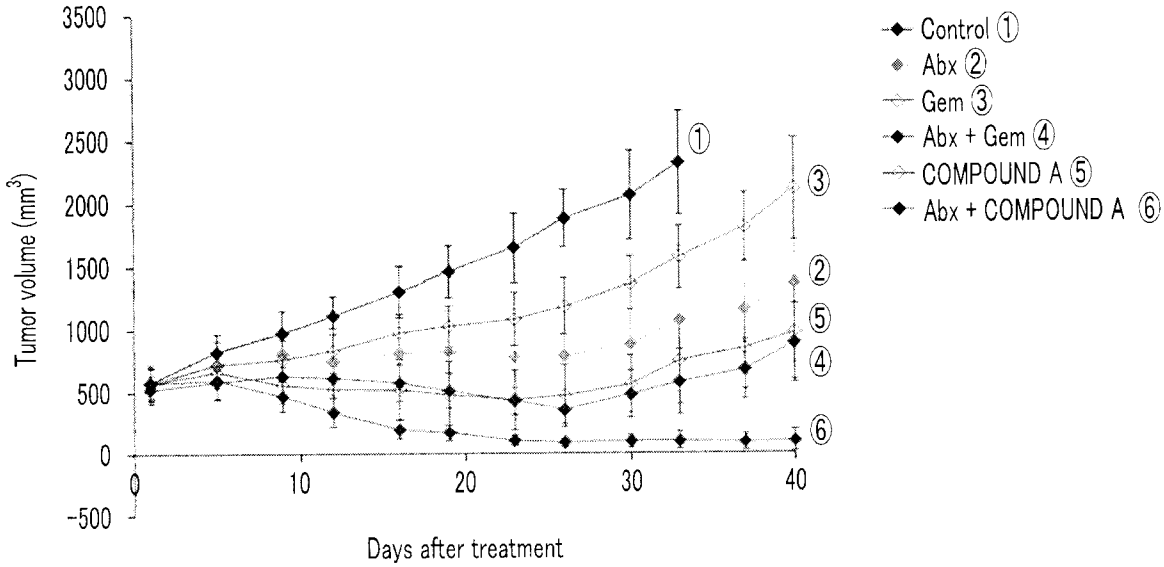

Tumor volume (mm3)
3500
3000
2500
2000
1500
1000
500
0
-500
0
10
20
30
40
Days after treatment
Control ①
Abx ②
Gem ③
Abx + Gem ④
COMPOUND A ⑤
Abx + COMPOUND A ⑥

FIG. 2

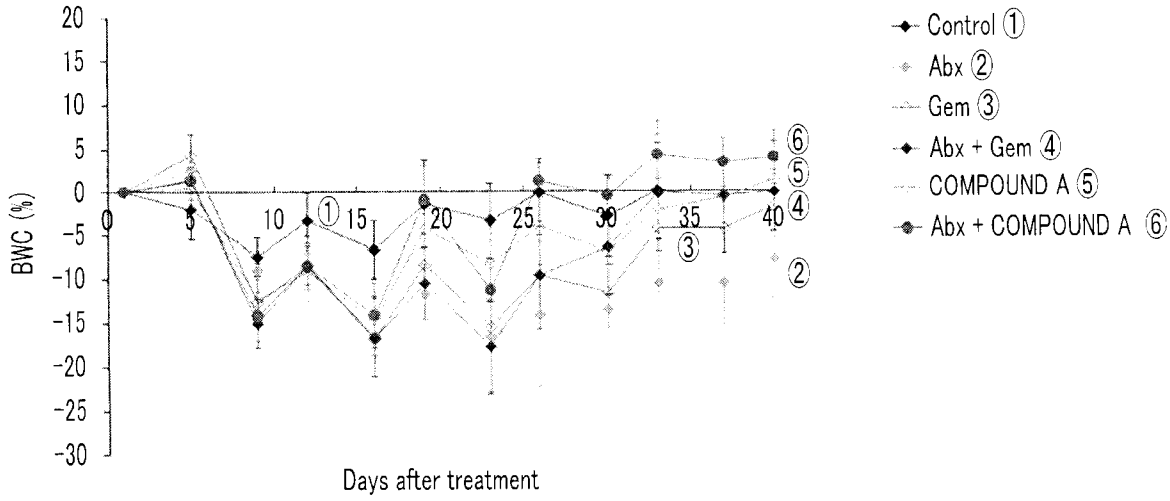
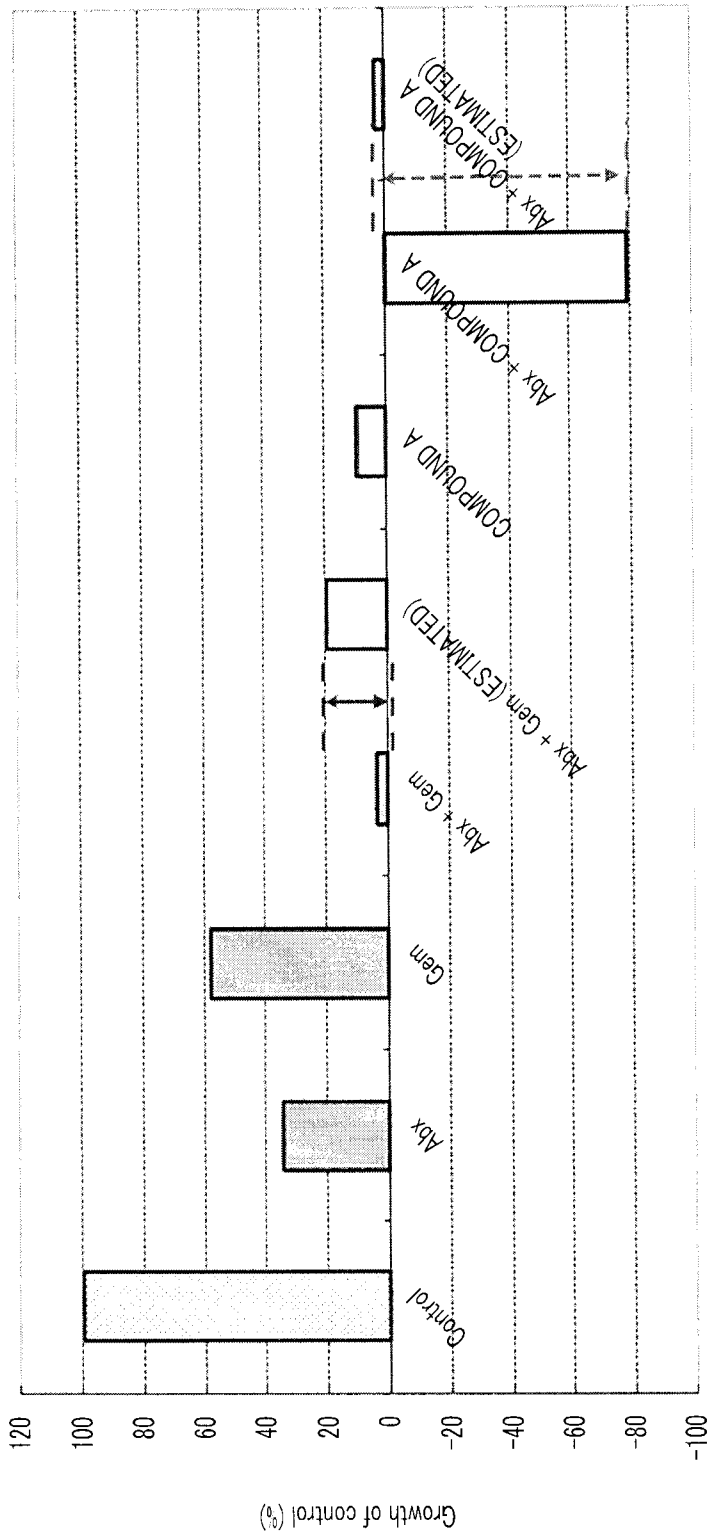

BWC (%)
20
15
10
5
0
-5
-10
-15
-20
-25
-30
0
5
10
15
20
25
30
35
40
Days after treatment
Control ①
Abx ②
Gem ③
Abx + Gem ④
COMPOUND A ⑤
Abx + COMPOUND A ⑥

FIG. 3


Control
Abx
Gem
Abx + Gem
Abx + Gem (ESTIMATED)
COMPOUND A
Abx + COMPOUND A
Abx + COMPOUND A (ESTIMATED)
120
100
80
60
40
20
0
-20
-40
-60
-80
-100
Growth of control (%)