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(54) **Title:** ANTITUMOR EFFECT POTENTIATOR AND ANTITUMOR AGENT

(54) 発明の名称: 抗腫瘍効果増強剤及び抗腫瘍剤

(57) **Abstract:** It is intended to provide: an antitumor effect potentiator containing a therapeutically efficacious amount of Tegafur, Gimeracil in an amount efficacious for potentiating the antitumor effect and Oteracil potassium in an amount efficacious in inhibiting side effects, characterized by containing at least one component selected from the group consisting of folinic acid and its pharmaceutically acceptable salts in an amount efficacious for potentiating the antitumor effect as the active ingredient; an antitumor agent characterized by containing a therapeutically efficacious amount of Tegafur, Gimeracil in an amount efficacious for potentiating the antitumor effect and Oteracil potassium in an amount efficacious in inhibiting side effects and , together with at least one component selected from the group consisting of folinic acid and its pharmaceutically acceptable salts in an amount efficacious for potentiating the antitumor effect as the active ingredient; a method of potentiating the antitumor effect of an antitumor agent characterized by comprising administering the above-described antitumor effect potentiator to a patient; and a method of treating cancer characterized by comprising administering the above antitumor agent to a patient.

(57) 要約: 本発明は、抗腫瘍効果増強のために有効な量のフォリン酸及びその薬学的に許容される塩からなる群から選ばれた少なくとも一種の成分を有効成分として含有することを特徴とする、治療に有効な量のテガフール、抗腫瘍効果増強のために有効な量のギメラシル及び副作用抑制のために有効な量のオテラシルカリウムを含有する抗腫瘍剤の抗腫瘍活性を増強させる抗腫瘍効果増強剤；治療に有効な量のテガフール、抗腫瘍効果増強のために有効な量のギメラシル、副作用抑制のために有効な量のオテラシルカリウム、並びに抗腫瘍効果増強のために有効な量のフォリン酸及びその薬学的に許容される塩からなる群から選ばれた少なくとも一種の成分、を有効成分として含有することを特徴とする抗腫瘍剤；上記抗腫瘍効果増強剤を患者に投与することを特徴とする抗腫瘍剤の抗腫瘍効果を増強させる方法；上記抗腫瘍剤を患者に投与することを特徴とする癌治療方法を提供するものである。

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DESCRIPTION

ANTITUMOR EFFECT POTENTIATOR AND ANTITUMOR AGENT

TECHNICAL FIELD

The present invention relates to an antitumor effect potentiator and an antitumor agent.

BACKGROUND ART

The research and development of antitumor agents has been actively pursued. A variety of effective antitumor agents are clinically used in the treatment of malignant tumors.

For example, tegafur is a drug that is activated *in vivo* and releases an active form, i.e., 5-fluorouracil (hereinafter referred to as "5-FU"), and is known as an improved antitumor agent that exhibits less toxicity and side effects than 5-FU itself. Moreover, a combined drug of tegafur and uracil is known to have a greater antitumor effect than tegafur alone. In particular, a combined drug having a tegafur to uracil molar ratio of 1 to 4 is commercially available as capsules and granules (trade name: UFT, manufactured by Taiho Pharmaceutical Co., Ltd.). This combined drug exhibits significantly enhanced antitumor effect compared with tegafur alone due to the fact that uracil, which does not have any antitumor effect by itself, inhibits the inactivation of 5-FU which is promptly metabolized and inactivated *in vivo*.

Japanese Patent Publication No. 2557303 discloses that the antitumor effect of an antitumor agent containing a combined drug of tegafur and uracil can be markedly potentiated without an increase in toxicity when it is used in combination with folinic acid or a salt thereof.

WO90/07334 discloses that the use of oxonic acid or a salt thereof in combination with 5-FU or a 5-FU derivative can inhibit the development of inflammation that may be caused by 5-FU or the 5-FU derivative.

Japanese Patent Publication No. 2614164 discloses an antitumor effect potentiator containing as active ingredients

2,4-dihydroxy-5-chloropyridine (gimeracil) and oxonic acid or a salt thereof which can increase the antitumor effect of tegafur while inhibiting side effects. It also discloses a 3-membered antitumor agent containing tegafur, gimeracil, and oxonic acid or a salt thereof as active ingredients. In particular, a combined drug containing tegafur, gimeracil, and oteracil potassium in a molar ratio of 1 : 0.4 : 1 is commercially available as capsules (trade name: TS-1, manufactured by Taiho Pharmaceutical Co., Ltd.). This antitumor agent has an enhanced antitumor effect due to the function of gimeracil, which exhibits a 5-FU degradation inhibitory effect about 200 times greater than that of uracil. Moreover, oxonic acid and salts thereof specifically inhibit the increase in gastrointestinal toxicity that is likely to be accompanied by the antitumor effect potentiation when tegafur and gimeracil are used in combination, thereby enhancing the therapeutic effect.

However, in view of the current state of cancer treatment, development of a pharmaceutical agent with a greater antitumor effect is required in order to completely inhibit the growth of tumors so as to prolong patient survival.

DISCLOSURE OF THE INVENTION

The present invention has been accomplished in view of the state of the art described above. A primary object of the invention is to provide a novel antitumor effect potentiator that can increase the antitumor effect of an antitumor agent containing tegafur, gimeracil, and oxonic acid or a salt thereof without aggravating side effects; and a novel antitumor agent with a high antitumor effect that contains the antitumor effect potentiator.

The inventors conducted extensive research to achieve the aforementioned object, and as a result, found that the use of folinic acid or a pharmacologically acceptable salt thereof, none of which have any antitumor effect by themselves, in combination with a 3-membered antitumor agent containing tegafur, gimeracil, and oteracil potassium, can markedly enhance the antitumor effect

of the antitumor agent without notably aggravating toxicity. The present invention has been accomplished based on this finding.

In particular, the present invention provides antitumor effect potentiators, antitumor agents, methods for treating cancer, and methods for enhancing an antitumor effect, etc., as described below.

1. An antitumor effect potentiator for enhancing antitumor activity of an antitumor agent comprising tegafur in a therapeutically effective amount, gimeracil in an amount effective for enhancing an antitumor effect, and oteracil potassium in an amount effective for inhibiting a side effect,

the antitumor effect potentiator comprising at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof in an amount effective for enhancing an antitumor effect.

2. The antitumor effect potentiator according to Item 1, wherein the antitumor agent comprises tegafur, gimeracil, and oteracil potassium in a tegafur : gimeracil : oteracil potassium molar ratio of 1 : 0.4 : 1.

3. An antitumor agent comprising, as active ingredients, tegafur in a therapeutically effective amount, gimeracil in an amount effective for enhancing an antitumor effect, oteracil potassium in an amount effective for inhibiting a side effect, and at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof in an amount effective for enhancing an antitumor effect.

4. The antitumor agent according to Item 3, wherein the antitumor agent is in a pharmaceutical preparation form comprising two or more separate preparations each of which contains one of the active ingredients consisting of tegafur, gimeracil, oteracil potassium, and at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof, or two or more of the active ingredients in any combination, or

in a pharmaceutical preparation form comprising a single preparation which contains all of the active ingredients.

5. The antitumor agent according to Item 3, wherein the amount of the active ingredients is such that, per mol of tegafur, gimeracil is in an amount of 0.1 to 5 mol, oteracil potassium is in an amount of 0.1 to 5 mol, and the at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof is in an amount of 0.01 to 10 mol.

6. The antitumor agent according to Item 5, wherein the active ingredients are contained in a molar ratio of tegafur : gimeracil : oteracil potassium : the at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof = 1 : 0.4 : 1 : 0.01 to 10.

7. The antitumor agent according to Item 3, wherein the antitumor agent is in a pharmaceutical preparation form comprising a combined preparation comprising 3 ingredients, i.e., tegafur, gimeracil and oteracil potassium, as active ingredients, and a pharmaceutical preparation comprising the at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof as an active ingredient.

8. A kit comprising a combination of pharmaceutical compositions for treating cancer in a mammal comprising:

(a) an antitumor composition comprising tegafur in a therapeutically effective amount, gimeracil in an amount effective for enhancing an antitumor effect, and oteracil potassium in an amount effective for inhibiting a side effect, and

(b) a composition comprising at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof in an amount effective for enhancing an antitumor effect of the antitumor composition.

9. A method for treating cancer in a mammal comprising the step of administering to the mammal tegafur in a therapeutically effective amount, gimeracil in an amount effective for enhancing an antitumor effect, oteracil potassium in an amount effective for inhibiting a side effect, and at least one member selected

from the group consisting of folinic acid and pharmacologically acceptable salts thereof in an amount effective for enhancing an antitumor effect.

10. A method for enhancing an antitumor effect when administering to a mammal an antitumor agent comprising tegafur in a therapeutically effective amount, gimeracil in an amount effective for enhancing an antitumor effect, and oteracil potassium in an amount effective for inhibiting a side effect,

the method comprising the step of administering to a patient at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof in an amount effective for enhancing the antitumor effect.

11. The method according to Item 10, wherein the at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof in an amount effective for enhancing an antitumor effect is administered to the patient concurrently with, or within 4 hours before or after, the administration of the antitumor agent comprising tegafur in a therapeutically effective amount, gimeracil in an amount effective for enhancing an antitumor effect, and oteracil potassium in an amount effective for inhibiting a side effect.

12. Use of at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof to produce an antitumor effect potentiator for enhancing an antitumor effect of an antitumor agent comprising tegafur in a therapeutically effective amount, gimeracil in an amount effective for enhancing an antitumor effect, and oteracil potassium in an amount effective for inhibiting a side effect.

13. Use of at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof to produce an antitumor agent with an enhanced antitumor effect that comprises tegafur in a therapeutically effective amount, gimeracil in an amount effective for enhancing an antitumor effect, and oteracil potassium in an amount effective for inhibiting a side effect.

14. Use of tegafur in a therapeutically effective amount, gimeracil in an amount effective for enhancing an antitumor effect, oteracil potassium in an amount effective for inhibiting a side effect, and at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof in an amount effective for enhancing an antitumor effect in the manufacture of a medicament for treating cancer.

15. Use of tegafur in a therapeutically effective amount, gimeracil in an amount effective for enhancing an antitumor effect, oteracil potassium in an amount effective for inhibiting a side effect, and at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof in an amount effective for enhancing an antitumor effect in the treatment of cancer.

16. A kit when used for treating cancer in a mammal comprising:

(a) an antitumor composition comprising tegafur in a therapeutically effective amount, gimeracil in an amount effective for enhancing an antitumor effect, and oteracil potassium in an amount effective for inhibiting a side effect, and

(b) a composition comprising at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof in an amount effective for enhancing an antitumor effect of the antitumor composition.

The antitumor effect potentiator of the present invention contains at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof as an active ingredient. Due to the administration of antitumor effect potentiator, the antitumor effect of an antitumor agent containing 3 ingredients, i.e., tegafur, gimeracil and oteracil potassium, as active ingredients can be significantly enhanced.

Folinic acid used as an active ingredient of the antitumor effect potentiator is a known compound and has been used as a toxicity reducing agent for folic acid antagonists. Folinic acid does not exhibit an antitumor effect by itself. There are two optical isomers of folinic acid, i.e., the *d*-isomer and the *l*-isomer. In the preset invention, the *d*-isomer and the *l*-isomer as well as a mixture of the *d*-isomer and the *l*-isomer are usable. In particular, it is preferable to use the *l*-isomer or a mixture of the *d*-isomer and the *l*-isomer. An example of pharmacologically acceptable salt of folinic acid is the calcium salt.

Tegafur (5-fluoro-1-(2-tetrahydrofuryl)-2,4-(1*H*,3*H*)-pyrimidinedione), an active ingredient of the antitumor agent, is a known compound, and is a drug activated *in vivo* and releases the active form, i.e., 5-FU. Tegafur can be produced according to known methods, for example, the method disclosed in Japanese Examined Patent Publication No. 1974-10510.

Gimeracil (2,4-dihydroxy-5-chloropyridine) is also a known compound, and although it does not exhibit any antitumor activity by itself, it can markedly potentiate an antitumor effect by inhibiting the *in vivo* metabolic inactivation of 5-FU.

Oteracil potassium (monopotassium 1,2,3,4-tetrahydro-2,4-dioxo-1,3,5-triazine-6-carboxylate) is also a known compound. Although it does not exhibit any antitumor activity by itself, it mostly distributes in the gastrointestinal tract and inhibits the activation of 5-FU at that location, thereby preventing gastrointestinal toxicity caused by 5-FU.

With respect to the antitumor agent containing 3

ingredients, i.e., tegafur, gimeracil and oteracil potassium, as active ingredients, the amount of each active ingredient may be within the ranges described in connection with known combined drugs, for example, that disclosed in Japanese Patent Publication No. 2614164. It is usually such that, per mole of tegafur, gimeracil is used in an amount of about 0.1 to about 5 mol and preferably about 0.1 to about 1.5 mol, and oteracil potassium in about 0.1 to about 5 mol and preferably about 0.2 to about 2 mol. A particularly preferable molar ratio of the 3 ingredients is tegafur : gimeracil : oteracil potassium = 1 : 0.4 : 1.

The antitumor agent containing 3 ingredients, i.e., tegafur, gimeracil and oteracil potassium, as active ingredients may be prepared in a pharmaceutical preparation form comprising two or more separate pharmaceutical preparations each of which contains one of the active ingredients or two or more of the active ingredients in any combination, or in a pharmaceutical preparation form comprising a single pharmaceutical preparation containing all of these active ingredients. In any case, such antitumor agents are prepared as pharmaceutical compositions according to standard methods using suitable pharmaceutical carriers. Carriers usable herein are those that are commonly used for known drugs, for example, excipients, binders, disintegrators, lubricants, colorants, taste enhancers, flavor enhancers, surfactants, etc.

When an antitumor agent in a pharmaceutical preparation form comprising two or more separate pharmaceutical preparations as described above is used, each pharmaceutical preparation may be administered concurrently, or one pharmaceutical agent may be administered any time before or after the administration of the other pharmaceutical preparation(s). Preferably, all of the pharmaceutical preparations are administered concurrently, or one pharmaceutical preparation is administered within 4 hours, and more preferably within 2 hours, before or after the administration of the other pharmaceutical preparation(s).

The antitumor effect potentiator comprising at least one member selected from the group consisting of folinic acid and

pharmacologically acceptable salts thereof as an active ingredient of the present invention may be independently prepared in various kinds of unit dosage form. In this case, the antitumor effect potentiator is prepared as a pharmaceutical preparation according to standard methods using suitable pharmaceutical carriers. Carriers usable herein are those that are commonly used for known drugs, for example, excipients, binders, disintegrators, lubricants, colorants, taste enhancers, flavor enhancers, surfactants, etc. The antitumor effect potentiator prepared in various kinds of unit dosage form may be administered concurrently with or separately from the antitumor agent containing 3 ingredients, i.e., tegafur, gimeracil and oteracil potassium, as active ingredients that may also be prepared in various kinds of unit dosage form. That is, the antitumor effect potentiator of the present invention can be administered any time before or after or concurrently with the administration of the antitumor agent containing 3 ingredients, i.e., tegafur, gimeracil and oteracil potassium, as active ingredients. Preferably, the antitumor effect potentiator is administered concurrently with or within 4 hours before or after the administration of the antitumor agent, and more preferably within 2 hours, before or after the administration of the antitumor agent.

When the antitumor effect potentiator of the present invention is administered concurrently with, or before or after, the administration of the aforementioned antitumor agent containing 3 ingredients, i.e., tegafur, gimeracil and oteracil potassium, as active ingredients, the antitumor effect potentiator is preferably administered in an amount such that the amount of the at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof, per mol of tegafur, is within the range of about 0.01 to about 10 mol, preferably about 0.05 to about 5 mol, and more preferably about 0.1 to about 2 mol.

According to the present invention, an antitumor agent containing an antitumor effect potentiator can be prepared, in

which at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof, i.e., an active ingredient of the aforementioned antitumor effect potentiator, is concomitantly present with an antitumor agent containing 3 ingredients, i.e., tegafur, gimeracil and oteracil potassium, as active ingredients. In this case, the antitumor agent may be in a combined pharmaceutical preparation form comprising a single pharmaceutical preparation containing all the active ingredients, i.e., tegafur, gimeracil and oteracil potassium, and at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof; or in a pharmaceutical preparation form comprising two or more separate preparations each of which contains one of the active ingredients or two or more of the active ingredients in any combination. In particular, the antitumor agent is preferably in a separate pharmaceutical preparation form comprising a combined preparation containing 3 ingredients, i.e., tegafur, gimeracil and oteracil potassium, as active ingredients and a pharmaceutical preparation containing at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof as an active ingredient.

The aforementioned antitumor agent containing at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof can be prepared in any unit dosage form for administration. It may be prepared as a pharmaceutical preparation according to known methods using suitable pharmaceutical carriers. Carriers usable herein are those that are heretofore used for known drugs, for example, excipients, binders, disintegrators, lubricants, colorants, taste enhancers, flavor enhancers, surfactants, etc.

With respect to the antitumor agent, the amounts of the ingredients are not limited. Usually, per mol of tegafur, gimeracil is in an amount of about 0.1 to about 5 mol and preferably about 0.1 to about 1.5 mol, oteracil potassium is in about 0.1 to about 5 mol and preferably about 0.2 to about 2 mol,

and the at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof is in about 0.01 to about 10 mol, preferably about 0.05 to about 5 mol and more preferably about 0.1 to about 2 mol. In particular, a preferable molar ratio of the ingredients is tegafur : gimeracil : oteracil potassium : the at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof = about 1 : 0.4 : 1 : 0.01 to 10, more preferably about 1 : 0.4 : 1 : 0.05 to 5, and particularly preferably about 1 : 0.4 : 1 : 0.1 to 2. When the antitumor agent is in a separate pharmaceutical preparation form in which a combined pharmaceutical preparation containing 3 ingredients, i.e., tegafur, gimeracil and oteracil potassium, as active ingredients and a pharmaceutical preparation containing at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof as an active ingredient are separately present as described above, the antitumor agent preferably contains the combined pharmaceutical preparation containing tegafur, gimeracil, and oteracil potassium in a molar ratio of 1 : 0.4 : 1, and the pharmaceutical preparation containing the at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof in an amount of about 0.01 to about 10 mol, preferably about 0.05 to about 5 mol, and more preferably about 0.1 to about 2 mol, per mol of tegafur.

According to the present invention, the antitumor effect potentiator and the combined agent containing tegafur, gimeracil, and oteracil potassium described above are applicable to a kit comprising a combination of pharmaceutical compositions for mammalian cancer treatment comprising:

(a) an antitumor composition containing tegafur in a therapeutically effective amount, gimeracil in an amount effective for enhancing an antitumor effect, and oteracil potassium in an amount effective for inhibiting a side effect, and

(b) a composition containing at least one member selected from

the group consisting of folinic acid and pharmacologically acceptable salts thereof in an amount effective for enhancing the antitumor effect of the antitumor composition. The compositions contained in such a kit may be in any known pharmaceutical preparation forms. The compositions are usually kept in any commonly used containers according to their pharmaceutical preparation form.

Such a kit is applicable to, for example, a kit for treatment of mammalian (including human) cancer that contains at least the 4 ingredients:

(i) tegafur in a therapeutically effective amount,

(ii) gimeracil in an amount effective for enhancing an antitumor effect,

(iii) oteracil potassium in an amount effective for inhibiting a side effect, these all being part of an antitumor composition, and

(iv) at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof in an amount effective for enhancing the antitumor effect of the antitumor composition, and that also contains

at least 2 containers for keeping these ingredients, in which tegafur and the at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof are kept in separate containers.

Unit dosage forms usable in administering the antitumor effect potentiator and antitumor agent of the present invention to treat malignant tumors of mammals, including humans, are not limited, and can be selected according to the purpose of the treatment. Specific examples are injections, suppositories, ophthalmic solutions, ointments, aerosols, and like parenteral forms; and tablets, coated tablets, powders, granules, capsules, fluids, pills, suspensions, emulsions, and like oral forms. The antitumor effect potentiator and the antitumor agent can be produced in such dosage forms according to methods heretofore known in this technical field.

In preparing solid oral agents, such as tablets,

powders, and granules, for example, the following can be used as carriers: lactose, saccharose, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, silicic acid, methylcellulose, glycerol, sodium alginate, gum arabic, and like excipients; simple syrups, liquid glucose, liquid starch, gelatin solutions, polyvinyl alcohol, polyvinyl ether, polyvinylpyrrolidone, carboxymethylcellulose, shellac, methylcellulose, ethylcellulose, water, ethanol, potassium phosphate, and like binders; dried starch, sodium alginate, powdered agar, powdered laminaran, sodium hydrogencarbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulfate, stearic acid monoglycerides, starch, lactose, and like disintegrators; saccharose, stearic acid, cocoa butter, hydrogenated oils, and like disintegration inhibitors; quaternary ammonium salts, sodium lauryl sulfate, and like absorption enhancers; glycerol, starch, and like humectants; starch, lactose, kaolin, bentonite, colloidal silicic acid, and like adsorbents; purified talc, stearic acid salts, powdered boric acid, polyethylene glycol, and like lubricants; etc. Furthermore, if necessary, tablets may be provided with a standard coating, for example, as sugar-coated tablets, gelatin-coated tablets, enteric-coated tablets, film-coated tablets, double-layer tablets, multi-layer tablets, and the like.

In preparing pills, glucose, lactose, starch, cacao butter, hydrogenated vegetable oils, kaolin, talc, and like excipients; powdered gum arabic, powdered tragacanth, gelatin, and like binders; laminaran, agar, and like disintegants; etc., can be used as carriers.

Capsules can be prepared by mixing the antitumor effect potentiator or the combined agent containing tegafur, gimeracil and oteracil potassium as well as the potentiator with the aforementioned various carriers and filling hard gelatin capsules, soft capsules or the like, with the mixture.

In preparing suppositories, polyethylene glycol, cacao butter, lanolin, higher alcohols, esters of higher alcohols, gelatin, semisynthetic glycerides, Witepsol (registered trademark,

Dynamite Nobel Inc.), etc., can be used as carriers.

In preparing injections, water, ethyl alcohol, macrogol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol, polyoxyethylene sorbitan fatty acid esters, and like diluents; sodium citrate, sodium acetate, sodium phosphate, and like pH-adjusters and buffers; sodium pyrosulfite, EDTA, thioglycolic acid, thiolactic acid, and like stabilizers; etc., can be used as carriers. In such cases, NaCl, glucose, or glycerol may be used in the pharmaceutical preparation in amounts sufficient to prepare an isotonic solution. Moreover, standard auxiliary dissolvents, soothing agents, topical anesthetics, etc., may be used. Subcutaneous, intramuscular, and intravenous injections can be prepared according to standard methods in conjunction with such carriers.

Liquid preparations may take the form of water-based or oil-based suspensions, solutions, syrups, or elixirs, and can be prepared according to standard methods using heretofore used additives.

In preparing the pharmaceutical preparation in the form of ointments such as pastes, creams, and gels, for example, white petrolatum, paraffin, glycerol, cellulose derivatives, polyethylene glycol, silicon, bentonite, etc., can be used as diluents.

The amount of the at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof, which is an active ingredient of the antitumor effect potentiator of the present invention, and the amounts of tegafur, gimeracil, oteracil potassium, and the at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof, which are active ingredients of the antitumor agent of the present invention, vary according to the dosage form, route of administration, dosing schedule, etc., and are not limited, and hence can be suitably selected. It is usually preferable that the active ingredients account for about 1 to about 70 wt.% of the pharmaceutical preparation.

The route of administration of the antitumor effect potentiator and the antitumor agent of the present invention are not limited and include, for instance, enteral administration, oral administration, rectal administration, intraoral administration, transdermal administration, etc. They can be determined according to the form of pharmaceutical preparation, the age, sex, and condition of the patient, and other factors. For example, tablets, pills, solutions, suspensions, emulsions, granules, capsules, and the like are administered orally; suppositories are administered intrarectally; and ointments are applied to the skin, the mucous membranes of the mouth, etc.

The dosage of each active ingredient in the present invention can be suitably selected according to the method of administration, the age, sex and other factors of the patient, the degree of the disease, etc. In oral administration, it is preferable to use the following ranges as a rough standard: the amount of tegafur is about 0.1 to about 100 mg/kg/day, preferably about 0.5 to about 30 mg/kg/day, and more preferably about 0.8 to about 20 mg/kg/day; the amount of gimeracil is about 0.05 to about 100 mg/kg/day, preferably about 0.1 to about 50 mg/kg/day, and more preferably about 0.2 to about 5 mg/kg/day; the amount of oteracil potassium is about 0.1 to about 100 mg/kg/day, preferably about 0.5 to about 40 mg/kg/day, and more preferably about 0.7 to about 20 mg/kg/day; and the amount of the at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof, calculated as the amount of folinic acid, is about 0.05 to about 1000 mg/kg/day, preferably about 0.1 to about 100 mg/kg/day, and more preferably about 0.2 to about 10 mg/kg/day.

The antitumor effect potentiator and the antitumor agent of the present invention can be administered in a single dose or in 2 to 4 divided doses per day. When in the form of an injectable solution for, for example, an intravenous injection, the antitumor effect potentiator and the antitumor agent, which if necessary may be diluted with a physiological saline or injectable glucose solution, can be gradually administered to an

adult over 5 minutes or longer, usually in an amount corresponding to about 0.5 to about 50 mg/kg/day of tegafur. When in the form of a suppository, the antitumor effect potentiator and the antitumor agent are administered to an adult once or twice a day at an interval of 6 to 12 hours usually in an amount corresponding to about 0.5 to about 100 mg/kg/day of tegafur by insertion into the rectum.

The types of malignant tumors treatable by the administration of the pharmaceutical preparation of the present invention are not limited, insofar as the active form, i.e., 5-fluorouracil, is reactive thereto; for example, head and neck cancers, stomach cancer, colon/rectal cancer (cancer of the large intestine), liver cancer, gallbladder/biliary cancer, pancreatic cancer, lung cancer, breast cancer, vesical cancer, prostatic cancer, uterine cancer, pharyngeal cancer, esophageal cancer, renal cancer, ovarian cancer, etc. In particular, a remarkable effect can be expected toward colon/rectal cancer (cancer of the large intestine), breast cancer, esophageal cancer, stomach cancer, head and neck cancers, and lung cancer.

According to the present invention, the antitumor effect of an antitumor agent containing 3 ingredients, i.e., tegafur, gimeracil and oteracil potassium, as active ingredients can be significantly strengthened without notably increasing toxicity, such as gastrointestinal toxicity, due to the use of a composition containing at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof as an antitumor effect potentiator.

BEST MODE FOR CARRYING OUT THE INVENTION

Examples are given below to illustrate the invention in more detail.

Example 1

A cubic fragment measuring about 2 mm in diameter of the human colon cancer cell line KM20C was subcutaneously implanted on the backs of male nude mice BALB/c-nu/nu. When the average tumor volume (= major axis (mm) x minor axis $(mm)^2$)

reached about 200 mm^3, the mice were divided into groups.

The following preparations each dissolved or suspended in a 0.5% hydroxypropylmethyl cellulose (HPMC) solution were orally administered to the mice once a day in amounts as shown in Table 1 for 9 consecutive days from the day after grouping: calcium folinate; a tegafur/gimeracil/oteracil potassium combined drug (molar ratio of tegafur : gimeracil : oteracil potassium = 1 : 0.4 : 1); a combined drug containing the tegafur/gimeracil/oteracil potassium combined drug described above and calcium folinate; a tegafur/uracil combined drug (molar ratio of tegafur : uracil = 1 : 4); and a combined drug containing the tegafur/uracil combined drug described above and calcium folinate.

The ratio of the tumor volume 10 days after grouping to the tumor volume upon grouping was calculated to obtain a relative tumor volume. The tumor growth inhibition ratio (%) was determined using the relative tumor volumes of the drug-administered groups and the control group.

The body weight change was calculated by subtracting the body weight of mice 10 days after the beginning of administration from the body weight of mice upon grouping and used as a parameter of whole-body toxicity of the pharmaceutical preparation. The results thus obtained are presented in Table 1. Although calcium folinate was used in the experiment, the dosage given in the table is that calculated as the amount of folinic acid.

Table 1

Drug	Dosage (mg/kg /day)	Dosage of folinic acid (mg/kg/day)	Relative tumor volume (Mean±SD)	Tumor growth inhibition ratio (%)	Body weight change (g)
none	0	0	2.38	-	-0.5
none	0	20.0	2.24	6.1	-0.8
Tegafur + gimeracil + oteracil potassium	8.3 + 2.4 + 8.1	0	1.76*	26.1	-1.7
Tegafur + gimeracil + oteracil potassium	8.3 + 2.4 + 8.1	20.0	1.35*#	43.3	-3.1
Tegafur + uracil	20.0 + 44.8	0	1.91*	19.7	-1.1
Tegafur + uracil	20.0 + 44.8	20.0	1.83*	23.3	-2.6

*: $p<0.05$, compared with the control group (the group not given any drug)

#: $p<0.05$, compared with the group given tegafur/gimeracil/oteracil potassium only

Example 2

A cubic fragment measuring about 2 mm in diameter of the human colon cancer cell line Colon 38 was subcutaneously implanted on the backs of male mice C57BL/6. When the average tumor volume (= major axis (mm) x minor axis $(mm)^2$) reached about 150 mm^3, the mice were divided into groups.

The following preparations each dissolved or suspended in a 0.5% hydroxypropylmethyl cellulose (HPMC) solution were orally administered to the mice once a day in amounts as shown in Table 2 for 9 consecutive days from the day after grouping: calcium folinate; a tegafur/gimeracil/oteracil potassium combined drug (molar ratio of tegafur : gimeracil : oteracil potassium = 1 : 0.4 : 1); a combined drug containing the tegafur/gimeracil/oteracil potassium combined drug described above and calcium folinate; a tegafur/uracil combined drug (molar ratio of tegafur : uracil = 1 : 4); and a combined drug containing the tegafur/uracil combined drug described above and calcium folinate.

The ratio of the tumor volume 12 days after grouping to the tumor volume upon grouping was calculated to obtain a relative tumor volume. The tumor growth inhibition ratio (%) was determined using the relative tumor volumes of the drug-

administered groups and the control group.

The body weight change was calculated by subtracting the body weight of mice 10 days after the beginning of administration from the body weight of mice upon grouping and used as a parameter of whole-body toxicity of the pharmaceutical preparation. The results thus obtained are presented in Table 2. Although calcium folinate was used in the experiment, the dosage given in the table is that calculated as the amount of folinic acid.

Table 2

Drug	Dosage (mg/kg /day)	Dosage of folinic acid (mg/kg/day)	Relative tumor volume (Mean±SD)	Tumor growth inhibition ratio (%)	Body weight change (g)
None	0	0	9.49	-	0.4
None	0	40.0	8.78	7.5	0.7
Tegafur + gimeracil + oteracil potassium	8.7 + 2.5 + 8.5	0	1.52*	84.0	0.9
Tegafur + gimeracil + oteracil potassium	8.7 + 2.5 + 8.5	40.0	0.86*#	91.0	0.7
Tegafur + uracil	15.1 + 33.8	0	2.60*	72.6	0.7
Tegafur + uracil	15.1 + 33.8	40.0	2.34*#	75.3	0.6

*: $p<0.05$, compared with the control group (the group not given any drug)

#: $p<0.05$, compared with the groups given either tegafur/gimeracil/oteracil potassium or tegafur/uracil

As is clear from Tables 1 and 2, the use of a tegafur/gimeracil/oteracil potassium combined drug in combination with calcium folinate can significantly enhance antitumor activity without substantially aggravating toxicity compared with the use of the tegafur/gimeracil/oteracil potassium combined pharmaceutical preparation alone. Moreover, this enhanced antitumor effect is substantially greater than that of the use of a tegafur/uracil combined drug in combination with calcium folinate.

Example 3

A cubic fragment measuring about 2 mm in diameter of

the human colon cancer cell line KM20C was subcutaneously implanted on the backs of male nude mice (BALB/cA-nu). When the average tumor volume (= major axis (mm) x minor axis $(mm)^2$) reached about 200 mm^3, the mice were divided into groups.

A combined drug containing a tegafur/gimeracil/oteracil potassium combined drug (molar ratio of tegafur : gimeracil : oteracil potassium = 1 : 0.4 : 1) and calcium folinate, dissolved or suspended in a 0.5% hydroxypropylmethyl cellulose (HPMC) solution was orally administered to the mice once a day in amounts as shown in Table 3 for 14 consecutive days from the day after grouping.

The ratio of the tumor volume 15 days after grouping to the tumor volume upon grouping was calculated to obtain a relative tumor volume. The tumor growth inhibition ratio (%) was determined using the relative tumor volumes of the drug-administered groups and the control group.

The body weight change was calculated by subtracting the body weight of mice 15 days after the beginning of administration from the body weight of mice upon grouping used as a parameter of whole-body toxicity of the pharmaceutical preparation. The results thus obtained are presented in Table 3. Although calcium folinate was used in the experiment, the dosage given in the table is that calculated as the amount of folinic acid.

Table 3

Drug	Dosage (mg/kg /day)	Dosage of folinic acid (mg/kg/day)	Relative tumor volume (Mean±SD)	Tumor growth inhibition ratio (%)	Body weight change (g)
None	0	0	4.75 ± 0.69	-	-0.3
None	0	20.0	4.50 ± 1.25	5.4	-0.6
Tegafur + gimeracil + oteracil potassium	5.7 + 1.7 + 5.6	0	3.48 ± 0.35*	26.9	-1.8
Tegafur + gimeracil + oteracil potassium	5.7 + 1.7 + 5.6	2.5	3.31 ± 0.38*	30.5	-1.1
Tegafur + gimeracil + oteracil potassium	5.7 + 1.7 + 5.6	5.0	2.85 ± 0.30*#	40.0	-2.3
Tegafur + gimeracil + oteracil potassium	5.7 + 1.7 + 5.6	10.0	2.61 ± 0.28*#	45.0	-2.2
Tegafur + gimeracil + oteracil potassium	5.7 + 1.7 + 5.6	20.0	2.55 ± 0.25*#	46.4	-1.8

*: $p<0.01$, compared with the control group (the group not given any drug)

#: $p<0.01$, compared with the group given tegafur/gimeracil/oteracil potassium only

The results of the investigation of the effect of calcium folinate dosage in enhancement of the antitumor effect of the tegafur/gimeracil/oteracil potassium combined drug using the human colon cancer cell line KM20C show some enhancement even at the dose of 2.5 mg/kg/day, and a clear enhancement at the dose of 5 mg/kg/day.

Formulation examples of the antimumor effect potentiator and the antitumor agent of the present invention are given below.

Formulation Example 1

Folinic acid	100 mg
Lactose	170 mg
Crystalline cellulose	77 mg
Magnesium stearate	3 mg
Amount per capsule	350 mg

Capsules were prepared according to a standard method using the formulation presented above.

Formulation Example 2

Calcium folinate	200 mg
Lactose	340 mg
Cornstarch	450 mg
Hydroxypropylmethyl cellulose	10 mg
Granules	1000 mg

Granules were prepared according to a standard method using the formulation presented above.

Formulation Example 3

Calcium folinate	500 mg
Lactose	240 mg
Cornstarch	250 mg
Hydroxypropylmethyl cellulose	10 mg
Powders	1000 mg

Powders were prepared according to a standard method using the formulation presented above.

Formulation Example 4

Folinic acid	50 mg
Lactose	90 mg
Crystalline cellulose	30 mg
Magnesium stearate	2 mg
Talc	3 mg
Hydroxypropylmethyl cellulose	10 mg
Amount per tablet	185 mg

Tablets were prepared according to a standard method using the formulation presented above.

Formulation Example 5

Calcium folinate	200 mg
Distilled water for injection	Suitable amount

Amount per ampule	5 ml

Injectable solutions were prepared according to a standard method using the formulation presented above.

Formulation Example 6

Tegafur	50 mg
Gimeracil	14.5 mg
Oteracil potassium	49 mg
Folinic acid	250 mg
Lactose	280 mg
Corn starch	298 mg
Hydroxypropylmethyl cellulose	10 mg
Amount per wrapper	951.5 mg

Granules were prepared according to a standard method using the formulation presented above.

Formulation Example 7

Tegafur	25 mg
Gimeracil	7.25 mg
Oteracil potassium	24.5 mg
Folinic acid	75 mg
Lactose	51 mg
Crystalline cellulose	28 mg
Magnesium stearate	5 mg
Amount per capsule	215.75 mg

Capsules were prepared according to a standard method using the formulation presented above.

Formulation Example 8

Tegafur	20 mg
Gimeracil	5.8 mg
Oteracil potassium	19.6 mg
Folinic acid	51 mg

Lactose	51 mg
Crystalline cellulose	15 mg
Magnesium stearate	3 mg
Cornstarch	14 mg
Hydroxypropylmethyl cellulose	10 mg
Amount per tablet	190.4 mg

Tablets were prepared according to a standard method using the formulation presented above.

Formulation Example 9

Tegafur	200 mg
Gimeracil	58 mg
Oteracil potassium	196 mg
Folinic acid	512 mg
Witepsol W-35	1034 mg
Amount per suppository	2000 mg

Suppositories were prepared according to a standard method using the formulation presented above.

It is to be understood that, if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art, in Australia or any other country.

In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprise" or variations such as "comprises" or "comprising" is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

Claims

1. An antitumor effect potentiator for enhancing antitumor activity of an antitumor agent comprising tegafur in a therapeutically effective amount, gimeracil in an amount effective for enhancing an antitumor effect, and oteracil potassium in an amount effective for inhibiting a side effect,

the antitumor effect potentiator comprising at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof in an amount effective for enhancing an antitumor effect.

2. The antitumor effect potentiator according to claim 1, wherein the antitumor agent comprises tegafur, gimeracil, and oteracil potassium in a tegafur : gimeracil : oteracil potassium molar ratio of 1 : 0.4 : 1.

3. An antitumor agent comprising, as active ingredients, tegafur in a therapeutically effective amount, gimeracil in an amount effective for enhancing an antitumor effect, oteracil potassium in an amount effective for inhibiting a side effect, and at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof in an amount effective for enhancing an antitumor effect.

4. The antitumor agent according to claim 3, wherein the antitumor agent is in a pharmaceutical preparation form comprising two or more separate preparations each of which contains one of the active ingredients consisting of tegafur, gimeracil, oteracil potassium, and at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof, or two or more of the active ingredients in any combination, or

in a pharmaceutical preparation form comprising a single preparation which contains all of the active ingredients.

5. The antitumor agent according to claim 3 or 4, wherein the amount of the active ingredients is such that, per mol of tegafur, gimeracil is in an amount of 0.1 to 5 mol, oteracil potassium is in an amount of 0.1 to 5 mol, and the at least one member selected from the group consisting of folinic acid and

pharmacologically acceptable salts thereof is in an amount of 0.01 to 10 mol.

6. The antitumor agent according to claim 5, wherein the active ingredients are contained in a molar ratio of tegafur : gimeracil : oteracil potassium : the at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof = 1 : 0.4 : 1 : 0.01 to 10.

7. The antitumor agent according to claim 3, wherein the antitumor agent is in a pharmaceutical preparation form comprising a combined preparation comprising 3 ingredients, i.e., tegafur, gimeracil and oteracil potassium, as active ingredients, and a pharmaceutical preparation comprising the at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof as an active ingredient.

8. A kit when used for treating cancer in a mammal comprising:

(a) an antitumor composition comprising tegafur in a therapeutically effective amount, gimeracil in an amount effective for enhancing an antitumor effect, and oteracil potassium in an amount effective for inhibiting a side effect, and

(b) a composition comprising at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof in an amount effective for enhancing an antitumor effect of the antitumor composition.

9. A method for treating cancer in a mammal comprising the step of administering to the mammal tegafur in a therapeutically effective amount, gimeracil in an amount effective for enhancing an antitumor effect, oteracil potassium in an amount effective for inhibiting a side effect, and at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof in an amount effective for enhancing an antitumor effect.

10. A method for enhancing an antitumor effect when administering to a mammal an antitumor agent comprising tegafur in a therapeutically effective amount, gimeracil in an amount effective for enhancing an antitumor effect, and oteracil potassium in an amount effective for inhibiting a side effect,

the method comprising the step of administering to a patient at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof in an amount effective for enhancing the antitumor effect.

11. The method according to claim 10, wherein the at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof in an amount effective for enhancing an antitumor effect is administered to the patient concurrently with, or within 4 hours before or after, the administration of the antitumor agent comprising tegafur in a therapeutically effective amount, gimeracil in an amount effective for enhancing an antitumor effect, and oteracil potassium in an amount effective for inhibiting a side effect.

12. Use of at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof to produce an antitumor effect potentiator for enhancing an antitumor effect of an antitumor agent comprising tegafur in a therapeutically effective amount, gimeracil in an amount effective for enhancing an antitumor effect, and oteracil potassium in an amount effective for inhibiting a side effect.

13. Use of at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof to produce an antitumor agent with an enhanced antitumor effect that comprises tegafur in a therapeutically effective amount, gimeracil in an amount effective for enhancing an antitumor effect, and oteracil potassium in an amount effective for inhibiting a side effect.

14. Use of tegafur in a therapeutically effective amount, gimeracil in an amount effective for enhancing an antitumor effect, oteracil potassium in an amount effective for inhibiting a side effect, and at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof in an amount effective for enhancing an antitumor effect in the manufacture of a medicament for treating cancer.

15. Use of tegafur in a therapeutically effective amount, gimeracil in an amount effective for enhancing an antitumor effect, oteracil potassium in an amount effective for inhibiting a side effect, and at least one member selected from the group consisting of folinic acid and pharmacologically acceptable salts thereof in an amount effective for enhancing an antitumor effect in the treatment of cancer.

16. An antitumor effect potentiator, substantially as herein described with reference to the accompanying examples, excluding comparative examples.

17. An antitumor agent, substantially as herein described with reference to the accompanying examples, excluding comparative examples.

18. A kit when used for treating cancer in a mammal or use, substantially as herein described with reference to the accompanying examples, excluding comparative examples.

19. A method for treating cancer, substantially as herein described with reference to the accompanying examples, excluding comparative examples.

20. A method for enhancing an antitumor effect, substantially as herein described with reference to the accompanying examples, excluding comparative examples.