

(19) **DANMARK**



Patent- og
Varemærkestyrelsen

(10) **DK/EP 1849470 T3**

(12) **Oversættelse af
europæisk patentskrift**

-
- (51) Int.Cl.: **A 61 K 31/7072 (2006.01)** **A 61 K 31/506 (2006.01)** **A 61 K 31/513 (2006.01)**
A 61 K 31/7068 (2006.01) **A 61 P 35/00 (2006.01)**
- (45) Oversættelsen bekendtgjort den: **2017-08-14**
- (80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2017-06-21**
- (86) Europæisk ansøgning nr.: **06712292.9**
- (86) Europæisk indleveringsdag: **2006-01-25**
- (87) Den europæiske ansøgnings publiceringsdag: **2007-10-31**
- (86) International ansøgning nr.: **JP2006301097**
- (87) Internationalt publikationsnr.: **WO2006080327**
- (30) Prioritet: **2005-01-26 US 42059** **2005-06-06 JP 2005165156**
- (84) Designerede stater: **AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI SK TR**
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- (54) Benævnelse: **ANTICANCERLÆGEMIDDEL INDEHOLDENDE ALPHA, ALPHA, ALPHA-TRIFLUORTHYIMIDIN OG THYIMIDINPHOSPHORYLASEINHIBITOR**
- (56) Fremdragne publikationer:
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Fortsættes ...

DESCRIPTION

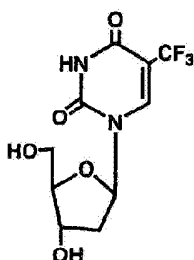
Technical Field

[0001] The present invention relates to a drug for the treatment of cancer (hereinafter may be referred to as "a cancer therapeutic drug") which is an anticancer agent containing α,α,α -trifluorothymidine (FTD) and a thymidine phosphorylase inhibitor (TPI) in combination, and exhibits enhanced cancer therapeutic effect.

Background Art

[0002] α,α,α -Trifluorothymidine (FTD, see the following structural formula) is a nucleoside analogue with substitution of a methyl group to trifluoromethyl group at the 5-position of thymidine, and was previously synthesized by Heidelberger, *et al.* (Non-Patent Documents 1 and 2).

[Formula 1]

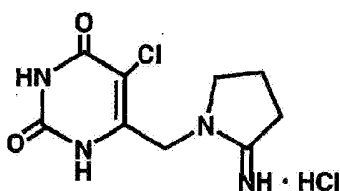


[0003] Unlike fluorouracil (FU)-based antitumor agents, which are widely used for cancer patients, FTD does not act on RNA, and is phosphorylated by intracellular thymidine kinase, thereby forming trifluorothymidine monophosphate (F_3TMP); i.e., a monophosphorylated form of FTD. F_3TMP binds to thymidylate synthase (TS), thereby exhibiting DNA synthesis inhibitory effect (Non-Patent Documents 3 and 4). An FU-based antitumor agent has been a drug of choice in clinical practice, and its main mechanism of action is considered TS inhibition; however, recent studies have revealed that some patients are less sensitive to the FU-based antitumor agent (Non-Patent Documents 5 to 7). In contrast, FTD, which is incorporated into DNA, has been considered to exhibit an antitumor effect different from that of an FU-based antitumor agent, and thus to become a clinically useful antitumor agent overcoming the aforementioned problem. However, clinical trials of FTD performed in the 1970s have indicated a problem associated with FTD itself; i.e., intravenously administered FTD is degraded by thymidine phosphorylase (TP) *in vivo*, resulting in a very short half-life of FTD in the blood (i.e., about 12 minutes) (Non-Patent Document 8). As has also been pointed out, although intravenous administration of FTD every three hours results in tumor-shrinking effect in some

patients, this administration means poses problems in that, for example, the means lacks flexibility in use and causes hematological toxicity and gastrointestinal toxicity, and the means does not necessarily contribute to survival period even in some patients showing tumor shrinkage (Non-Patent Document 9).

[0004] In order to maintain blood FTD level and to realize oral administration of FTD for improving flexibility in use, the present applicant previously found that 5-chloro-6-(1-(2-iminopyrrolidinyl)methyl)uracil hydrochloride (see the following structural formula) serves as a thymidine phosphorylase inhibitor (TPI) for suppressing degradation of FTD; and developed a cancer therapeutic drug containing FTD and the TPI in a molar ratio of 1 : 0.5 (TAS-102) (Patent Document 1 and Non-Patent Document 10).

[Formula 2]



[0005] A phase I clinical trial of this combination drug was carried out in the USA. The trial, which was initiated by once-a-day oral administration, showed that blood FTD level was maintained, and this combination drug could be orally administered. However, this combination drug failed to exhibit a clinically satisfactory cancer therapeutic effect.

Non-Patent Document 1: J. Am. Chem. Soc., 84: 3597-3598, 1962

Non-Patent Document 2: J. Med. Chem., 7: 1-5, 1964

Non-Patent Document 3: Biochemistry, 33: 15086-15094, 1994

Non-Patent Document 4: Mol. Pharmacol., 1: 14-30, 1965

Non-Patent Document 5: J. Clin. Oncol., 12: 2640-2647, 1994

Non-Patent Document 6: J. Clin. Oncol., 14: 176-182, 1996

Non-Patent Document 7: J. Clin. Oncol., 21: 815-819, 2003

Non-Patent Document 8: Cancer Res., 32: 247-253, 1972

Non-Patent Document 9: Cancer Chemother. Rep., 55: 205-208, 1971

Non-Patent Document 10: International Journal of Oncology 25: 571-578, 2004

Patent Document 1: Japanese Patent No. 3088757. Emura et al., International journal of molecular medicine, vol. 13, no 2, 2004, pages 249-255, discloses a dosing schedule for TAS-102 based on its intracellular metabolism and its incorporation into DNA.

Disclosure of the Invention

Problems to be Solved by the Invention

[0006] In view of the foregoing, an object of the present invention is to provide a cancer therapeutic drug exhibiting higher efficacy.

Means for Solving the Problems

[0007] In order to achieve the aforementioned object, the present inventors have changed the dosage schedule of the above-described combination drug so that the drug is orally administered to a human twice daily. As a result, the inventors have found that, quite unexpectedly, administration of the drug at a low daily dose of 20 to 80 mg/m² (as a dose of FTD) exhibits remarkable anticancer effect, although it is that once-a-day administration of the drug requires a daily dose of 100 mg/m² (as a dose of FTD). The present invention has been accomplished on the basis of this finding.

[0008] Accordingly, the present invention provides a cancer therapeutic drug, which is a composition containing alpha, alpha, alpha-trifluorothymidine (FTD) and 5-chloro-6-(1-(2-iminopyrrolidinyl)methyl)uracil hydrochloride (hereinafter may be referred to as "TPI-1") in a molar ratio of 1 : 0.5 (hereinafter the composition may be referred to as "TAS-102") for use in the treatment of cancer in a human patient in need thereof by orally administering the drug at a dose, as dose of FTD, of 20 to 80 mg/m²/day twice daily. The present disclosure also relates to the use of a composition containing α,α,α -trifluorothymidine (FTD) and 5-chloro-6-(1-(2-iminopyrrolidinyl)methyl)uracil hydrochloride in a molar ratio of 1 : 0.5 for producing a cancer therapeutic drug which is orally administered to a patient in need thereof at a dose, as dose of FTD, of 20 to 80 mg/m²/day twice daily to four times daily.

[0009] The present disclosure also relates to a method for treatment of cancer, characterized in that the method comprises orally administering a composition containing α,α,α -trifluorothymidine (FTD) and 5-chloro-6-(1-(2-iminopyrrolidinyl)methyl)uracil hydrochloride in a molar ratio of 1 : 0.5 to a patient in need thereof at a dose, as dose of FTD, of 20 to 80 mg/m²/day twice daily to four times daily.

Effects of the Invention

[0010] According to the present invention, even when the total daily dose of the cancer therapeutic drug is lower than that in the case of once-a-day administration, more excellent cancer therapeutic effect is obtained.

Brief Description of the Drawings

[0011]

[Fig. 1] Fig. 1 shows comparison of therapeutic effect of a TAS-102 preparation containing FTD and TPI-1 on gastrointestinal cancer patients between the case of oral administration thrice a day and the case of oral administration once a day (PD: progressive disease, SD: stable disease, MR: minor response, PR: partial response). The vertical axis represents individual patients, whereas the horizontal axis represents the number of treatment courses. In one treatment course (a total of four weeks), a weekly dosage cycle consisting of five-day administration and two-day rest is carried out for two weeks, followed by rest for two weeks. If necessary, the rest period may be gradually prolonged in consideration of, for example, the health condition of patients and the degree of side effects or the like.

[Fig. 2] Fig. 2 shows comparison of therapeutic effect of a TAS-102 preparation containing FTD and TPI-1 on breast cancer patients in the case of oral administration twice a day (PD: progressive disease, SD: stable disease, MR: minor response, PR: partial response). The vertical axis represents individual patients, whereas the horizontal axis represents the number of treatment courses. The treatment course is the same as described above.

Best Modes for Carrying Out the Invention

[0012] The composition used in the present invention contains FTD and TPI-1 in a molar ratio of 1 : 0.5. FTD (i.e., α,α,α -trifluorothymidine) is a drug which inhibits growth of cancer cells through the following mechanism: FTD is phosphorylated by intracellular thymidine kinase, thereby forming F_3TMP , and the thus-formed F_3TMP binds to thymidine synthase, thereby exhibiting DNA synthesis inhibitory effect. Meanwhile, TPI-1 is a drug which prevents inactivation of FTD due to degradation by inhibiting thymidine phosphorylase, which is a degradative enzyme for FTD.

[0013] No particular limitation is imposed on the composition, so long as it can be orally administered. The composition may be in the form of a single preparation containing both FTD and TPI-1, or combination of an FTD-containing preparation and a TPI-1-containing preparation. Examples of the form of such a preparation include tablets, coated tablets, pills, powders, granules, capsules, solutions, suspensions, and emulsions or the like. Such

preparations may be formulated by use of, for example, a pharmaceutically acceptable carrier and the like through a conventional formulation method which is generally known in the art. Such a preparation may be appropriately divided and packaged so that a dose of 20 to 80 mg/m²/day is administered twice daily. No particular limitation is imposed on the method for packaging a preparation, so long as the method is an established method generally known in the art. For example, a tablet may be packaged in a material used for moisture- and oxygen-impervious packaging.

[0014] Examples of carriers which may be used for forming tablets include excipients such as lactose, sucrose, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, and silicic acid; binders such as water, ethanol, propanol, cornstarch, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethylcellulose, shellac, methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, potassium phosphate, and polyvinylpyrrolidone; disintegrators such as dry starch, sodium alginate, agar powder, laminaran powder, sodium hydrogencarbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulfate, monoglyceride stearate, starch, and lactose; disintegration inhibitors such as sucrose, stearic acid, cacao butter, and hydrogenated oil; absorption promoters such as quaternary ammonium bases and sodium lauryl sulfate; humectants such as glycerin and starch; adsorbents such as starch, lactose, kaolin, bentonite, and colloidal silicic acid; and lubricants such as purified talc, stearic acid salts, boric acid powder, and polyethylene glycol. The tablets may be optionally coated with a conventional coating, and examples of such coated tablets include sugar-coated tablets, gelatin-coated tablets, enteric-coated tablets, film-coated tablets, double-layer tablets, and multi-layer tablets.

[0015] Examples of carriers which may be used for forming a pills include excipients such as glucose, lactose, starch, cacao butter, hydrogenated vegetable oil, kaolin, and talc; binders such as powdered acacia, powdered tragacanth, gelatin, and ethanol; and disintegrators such as laminaran and agar.

[0016] A capsule is prepared through an ordinary method by mixing the aforementioned active ingredients with any of the above-exemplified carriers, and by filling the resultant mixture into, for example, a hard gelatin capsule or a soft capsule.

[0017] An oral liquid preparation (e.g., an oral solution, a syrup, or an elixir) may be prepared through an ordinary method by use of, for example, a flavoring agent, a buffer, a stabilizer, or a smell correcting agent. Examples of the flavoring agent include sucrose, bitter orange peel, citric acid, and tartaric acid; examples of the buffer include sodium citrate; and examples of the stabilizer include tragacanth, gum arabic, and gelatin.

[0018] If necessary, each of the aforementioned preparations may contain an additional additive such as a coloring agent, a preservative, a perfume, a seasoning agent, or a sweetener, or an additional pharmaceutical drug.

[0019] The composition of the present invention is orally administered at a dose of 20 to 80

mg/m²/day (as a dose of FTD) twice daily. The daily dose is more preferably 25 to 75 mg/m²/day, much more preferably 30 to 75 mg/m²/day, particularly preferably 50 to 70 mg/m²/day, as a dose of FTD. Dose of the composition administered to a patient in need thereof is determined on the basis of the body surface area (BSA) of the patient calculated from the patient's height and body weight. Body surface area of a patient is calculated through a conventional method which is appropriately selected in consideration of, for example, the race, sex, health condition, and symptom of the patient. Body surface area is calculated by use of, for example, any of the following calculation formulas 1 to 5, preferably the formula 1 or 2(a).

1. 1. The Mosteller formula (see N. Engl. J. Med. 1987 Oct 22; 317 (17): 1098 (letter))

$$\text{BSA (m}^2\text{)} = ([\text{height (cm)} \times \text{weight (kg)}] / 3600)^{1/2}$$
2. 2. The DuBois and DuBois formula (see Arch. Int. Med. 1916 17: 863-71; J. Clin. Anesth. 1992; 4 (1): 4-10)
 1. (a) $\text{BSA (m}^2\text{)} = 0.20247 \times \text{height (m)}^{0.725} \times \text{weight (kg)}^{0.425}$
 2. (b) $\text{BSA (m}^2\text{)} = 0.007184 \times \text{height (cm)}^{0.725} \times \text{weight (kg)}^{0.425}$
3. 3. The Haycock formula (see The Journal of Pediatrics 1978 93: 1: 62-66)

$$\text{BSA (m}^2\text{)} = 0.024265 \times \text{height (cm)}^{0.3964} \times \text{weight (kg)}^{0.5378}$$
4. 4. The Gehan and George formula (see Cancer Chemother. Rep. 1970 54: 225-35)

$$\text{BSA (m}^2\text{)} = 0.0235 \times \text{height (cm)}^{0.42246} \times \text{weight (kg)}^{0.51456}$$
5. 5. The Boyd formula (see Minneapolis: University of Minnesota Press, 1935)

$$\text{BSA (m}^2\text{)} = 0.0003207 \times \text{height (cm)}^{0.3} \times \text{weight (grams)}^{(0.7285 - (0.0188 \times \text{LOG(grams)})}$$

[0020] When, for example, body surface area of a cancer patient having a height of 175 cm and a body weight of 70 kg is calculated by use of the aforementioned calculation formula 1, the body surface area is determined to be $([175 \text{ (cm)} \times 70 \text{ (kg)}] / 3600)^{1/2} = 1.84 \text{ (m}^2\text{)}$. When a dose of 60 mg/m²/day is applied to the patient, the total daily dose is determined to be about 110 mg (i.e., $1.84 \times 60 = 111 \text{ mg}$), and this daily dose is administered twice daily to four times daily.

[0021] In the present invention, the composition is orally administered at a dose of 20 to 80 mg/m²/day (as a dose of FTD) twice daily. Preferably, the composition is administered at intervals of six hours or more.

[0022] In the present invention, a weekly dosage schedule may consist of daily administration, but preferably, the schedule consists of five-day administration and two-day rest, from the viewpoint of reduction of burden on patients. More preferably, a weekly dosage cycle consisting of five-day administration and two-day rest is carried out for two weeks, followed by rest for two weeks.

[0023] Examples of the cancer to which the cancer therapeutic drug of the present invention is applied include, but are not particularly limited to, esophageal cancer, gastric cancer, liver cancer, gallbladder/bile duct cancer, pancreatic cancer, colorectal cancer, head and neck cancer, lung cancer, breast cancer, cervical cancer, ovarian cancer, bladder cancer, prostate cancer, testicular tumor, soft tissue and bone sarcoma, skin cancer, malignant lymphoma, leukemia, and brain tumor. Preferred are malignant solid cancers such as gastric cancer, pancreatic cancer, breast cancer, colorectal cancer, head and neck cancer, gallbladder/bile duct cancer, and lung cancer.

[0024] According to the present invention, even when the therapeutic drug is administered at a dose lower than that in the case of conventional once-a-day administration, very excellent cancer therapeutic effect is obtained. This is because, the amount of FTD incorporated into target site DNA is increased through administration twice daily. In addition, the method of the present invention facilitates control of side effects.

Examples

[0025] The present invention will next be described in more detail by way of examples.
Formulation Example 1.

FTD	20.00 mg
TPI-1	9.42 mg
Lactose	70.00 mg
Crystalline cellulose	3.50 mg
Magnesium stearate	1.00 mg
Talc	1.00 mg
Cornstarch	3.50 mg
Hydroxypropylmethylcellulose	25.00 mg
Total weight (per tablet)	133.42 mg

[0026] Tablets were prepared from the aforementioned formulation ratio according to an ordinary method.

Formulation Example 2.

FTD	15.00 mg
TPI-1	7.07 mg
Lactose	45.00 mg
Carboxymethylcellulose	5.00 mg
Magnesium stearate	2.00 mg

Titanium oxide	0.50 mg
Hydroxypropylmethylcellulose	1.00 mg
Polyethylene glycol 4000	0.50 mg
Total weight (per tablet)	85.07 mg

[0027] Tablets were prepared from the aforementioned formulation ratio according to an ordinary method.

Formulation Example 3.

FTD	30.00 mg
TPI-1	14.13 mg
Lactose	85.00 mg
Cornstarch	100.00 mg
Hydroxypropylcellulose	2.50 mg
Total weight (per package)	231.63 mg

[0028] Granules were prepared from the aforementioned formulation ratio according to an ordinary method.

Formulation Example 4.

FTD	10.00 mg
TPI-1	4.71 mg
Lactose	24.00 mg
Crystalline cellulose	12.50 mg
Magnesium stearate	1.00 mg
Total weight (per capsule)	52.21 mg

[0029] Capsules were prepared from the aforementioned formulation ratio according to an ordinary method.

Example 1. (Reference Example)

[0030] Therapeutic effect of TAS-102 was studied by orally administering TAS-102 to cancer patients at a dose of 100 mg/m² (as a dose of FTD) once a day (trial 1), or at a dose of 70 mg/m² (as a dose of FTD) thrice a day (trial 2).

[0031] These trials were performed in patients with gastrointestinal cancer for which standard

therapy is ineffective or no curative therapy exists, for the main purpose of evaluating safety of TAS-102. The trials correspond to a phase I clinical trial for determining the recommended dose (RD) of TAS-102 at which the drug can be safely administered without causing problematic side effects in phase II clinical trials carried out in each of different cancer types. If possible, therapeutic effect of the drug on tumor is evaluated through the trials. For evaluation of therapeutic effect on tumor, the tumor-shrinking effect of the drug was determined on the basis of comprehensive evaluation of target lesions (i.e., lesions having a size equal to or greater than a measurable size corresponding to slice thickness in CT or a similar technique) and non-target lesions (i.e., all lesions other than the target lesions) with reference to the RECIST evaluation method (Journal of the National Cancer Institute, 2000, Vol. 92, No. 3, 205-216). In the trials, "PR (partial response)" refers to the case where the sum of the major axis lengths of target lesions is reduced by 30% or more as compared with that before administration of the drug, and the effect of the drug is maintained for a predetermined period of time (generally four weeks) during which no exacerbation of non-target lesions is observed. "PD (progressive disease)" refers to the case where the sum of the major axis lengths of target lesions is increased by 20% or more as compared with the minimum sum of the major axis lengths as recorded after initiation of the trials, or the case where existing non-target lesions are apparently exacerbated or new lesions are observed. "SD (stable disease)" refers to the case where tumor shrinkage is not enough to be regarded as "PR," whereas tumor progression is not enough to be regarded as "PD"; i.e., progression of tumor is stopped, and no exacerbation of tumor is observed. "MR (minor response)" refers to the case where tumor-shrinking effect is lower as compared with that of "PR" (i.e., reduction in the sum of the lesion major axis lengths is less than 30%), but is maintained at a comparable level (i.e., reduction in the sum of the lesion major axis lengths is about 15%), or the case where therapeutic effect corresponding to "PR" is observed temporarily.

[0032] The results are shown in Fig. 1. In Fig. 1, "Trial 1" corresponds to administration of a TAS-102 preparation (tablets) at a dose of 100 mg/m² (as a dose of FTD) once a day (five-day administration and two-day rest per week). The data show that the drug administration was effective (i.e., stable disease without exacerbation of tumor) for two of six patients (33%). "Trial 2" corresponds to administration of a TAS-102 preparation (tablets) at a dose of 70 mg/m² (as a dose of FTD) thrice daily (five-day administration and two-day rest per week). The data show that the drug administration was effective for four of six patients (67%). Specifically, in the four patients, progression of tumor was stopped, and no exacerbation of tumor was observed; and, in one of the four patients, tumor shrinkage was also observed. Thus, these data suggest that administration of TAS-102 in a divided manner is an effective administration method for patients with gastrointestinal cancer for which standard therapy is ineffective or no curative therapy exists.

Example 2.

[0033] Similar to the case of Example 1, phase I clinical trials were performed in breast cancer

patients.

[0034] Therapeutic effect of TAS-102 was studied by orally administering TAS-102 to patients with breast cancer for which standard therapy is ineffective or no curative therapy exists at a dose of 60 mg/m²/day (as a dose of FTD) twice a day (trial 3), or at a dose of 50 mg/m²/day (as a dose of FTD) twice a day (trial 4).

[0035] The results are shown in Fig. 2. "Trial 3" corresponds to administration of a TAS-102 preparation (tablets) at a dose of 60 mg/m² (as a dose of FTD) twice daily (five-day administration and two-day rest per week). The data show that the drug administration was effective for five of seven patients (71%). "Trial 4" corresponds to administration of a TAS-102 preparation (tablets) at a dose of 50 mg/m² (as a dose of FTD) twice daily (five-day administration and two-day rest per week). The data show that the drug administration was effective for seven of nine patients (78%). Specifically, in most patients, progression of tumor was stopped, and no exacerbation of tumor was observed. In a plurality of patients, SD was continued for six months or more, and, in one patient, SD was continued for one year or more. In breast cancer therapy, a therapeutic method which can be continuously carried out for six courses (about six months) or more is considered to have high clinical utility. Thus, these data suggest that, similar to the case of Example 1, administration of TAS-102 in a divided manner is an effective administration method for patients with breast cancer for which standard therapy is ineffective or no curative therapy exists.

REFERENCES CITED IN THE DESCRIPTION

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Patentkrav

- 5 **1.** Terapeutisk cancerlægemiddel, som er en sammensætning omfattende α,α,α -trifluorthymidin (FTD) og 5-chlor-6-(1-(2-iminopyrrolidinyl)methyl)uracilhydrochlorid i et molforhold på 1 : 0,5, til anvendelse ved behandling af cancer hos en patient, der er et menneske, med behov herfor ved oral indgivelse af lægemidlet i en dosis, som en dosis af FTD, på 20 til 80 mg/m²/dag, to gange dagligt.
- 10 **2.** Terapeutisk cancerlægemiddel til anvendelse ifølge krav 1, hvor lægemidlet indgives oralt til en patient med behov herfor i en dosis, som en dosis af FTD, på 25 til 75 mg/m²/dag, indgivet to gange dagligt.
- 15 **3.** Terapeutisk cancerlægemiddel til anvendelse ifølge krav 1, hvor lægemidlet indgives to gange dagligt i henhold til en ugebaseret plan, der indbefatter indgivelse i fem dage og to dages pause.
- 20 **4.** Terapeutisk cancerlægemiddel til anvendelse ifølge krav 1, hvor lægemidlet indgives på en sådan måde, at en ugentlig doseringscyklus bestående af indgivelse i fem dage og to dages pause udføres i to uger, efterfulgt af pause i to uger.
- 25 **5.** Terapeutisk cancerlægemiddel til anvendelse ifølge krav 1, hvor lægemidlet indgives til en patient med behov herfor i en dosis, som en dosis af FTD, på FTD, på 50 til 70 mg/m²/dag.
- 30 **6.** Terapeutisk cancerlægemiddel til anvendelse ifølge krav 1 til 5, hvor lægemidlet indgives til en patient med behov herfor i en dosis, som en dosis af FTD, på 70 mg/m²/dag.
- 35 **7.** Terapeutisk cancerlægemiddel til anvendelse ifølge et hvilket som helst af kravene 1 til 6, hvor den cancer, som det terapeutiske cancerlægemiddel anvendes mod, indbefatter øsofaguxcancer, gastrisk cancer, levercancer, galdeblære-/galdevejscancer, pancreascancer, kolorektal cancer, hoved- og halscancer, lungecancer, brystcancer, cervixcancer, ovariecancer, blærecancer, prostatacancer, testikeltumor, bløddels- og knoglesarkom, hudcancer,

malignt lymfom, leukæmi og hjernetumor.

5 **8.** Terapeutisk cancerlægemiddel til anvendelse ifølge et hvilket som helst af kravene 1 til 7, hvor den cancer, som det terapeutiske cancerlægemiddel anvendes mod, indbefatter maligne solide cancere udvalgt blandt gastrisk cancer, pancreascancer, brystcancer, kolorektal cancer, hoved- og halscancer, galdeblære-/galdevejscancer og lungecancer.

10 **9.** Terapeutisk cancerlægemiddel til anvendelse ifølge et hvilket som helst af kravene 1 til 8, hvor dosen af sammensætningen, der indgives til en patient med behov herfor, bestemmes på basis af patientens legemsoverflade, hvilken legemsoverflade beregnes ved anvendelse af en hvilken som helst af de følgende beregningsformler 1 til 5:

15 **1.** Mosteller-formlen (jf. N. Engl. J. Med. 1987 Oct 22; 317 (17): 1098 (letter))

$$\text{Legemsoverflade (m}^2\text{)} = ([\text{højde (cm)} \times \text{vægt (kg)}] / 3600)^{1/2}$$

2. DuBois og DuBois-formlen (jf. Arch. Int. Med. 1916 17: 863-71; J. Clin. Anesth. 1992; 4 (1): 4-10)

(a) $\text{legemsoverflade (m}^2\text{)} = 0,20247 \times \text{højde (m)}^{0,725} \times \text{vægt (kg)}^{0,425}$

(b) $\text{legemsoverflade (m}^2\text{)} = 0,007184 \times \text{højde (cm)}^{0,725} \times \text{vægt (kg)}^{0,425}$

20 **3.** Haycock-formlen (jf. The Journal of Pediatrics 1978 93: 1: 62-66)

$$\text{Legemsoverflade (m}^2\text{)} = 0,024265 \times \text{højde (cm)}^{6,3964} \times \text{vægt (kg)}^{0,5378}$$

4. Gehan and George-formlen (jf. Cancer Chemother. Rep. 1970 54: 225-35)

$$\text{Legemsoverflade (m}^2\text{)} = 0,0235 \times \text{højde (cm)}^{0,42246} \times \text{vægt (kg)}^{0,51456}$$

5. Boyd-formlen (jf. Minneapolis: University of Minnesota Press, 1935)

25
$$\text{Legemsoverflade (m}^2\text{)} = 0,0003207 \times \text{højde (cm)}^{0,3} \times \text{vægt (gram)}^{(0,7285 - (0,0188 \times \text{LOG (gram)})}$$

30

DRAWINGS

Fig. 1

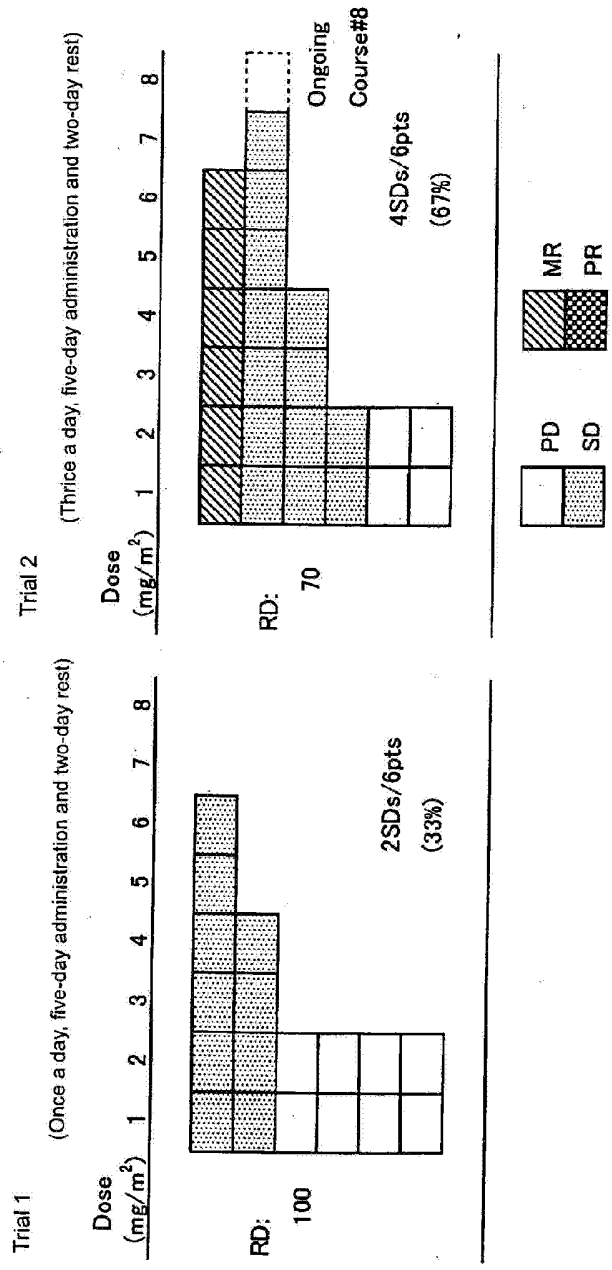
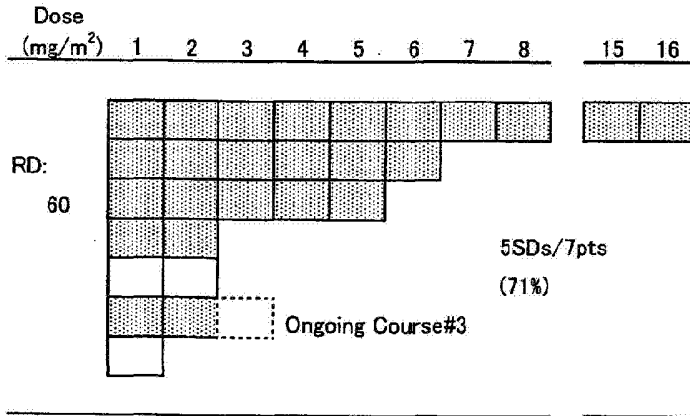


Fig. 2

Trial 3

(Twice a day, five-day administration and two-day rest)



Trial 4

(Twice a day, five-day administration and two-day rest)

