(19) DANMARK

(10) DK/EP 2059254 T3

(12) Oversættelse af europæisk patentskrift

Patent- og Varemærkestyrelsen

(51) Int.Cl.: *A 61 K 38/22 (2006.01)* *A 61 P 35/00 (2006.01)*

(45) Oversættelsen bekendtgjort den: **2015-07-13**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2015-04-08**

(86) Europæisk ansøgning nr.: **07841411.7**

(86) Europæisk indleveringsdag: **2007-08-27**

(87) Den europæiske ansøgnings publiceringsdag: **2009-05-20**

(86) International ansøgning nr.: **US2007076903**

(87) Internationalt publikationsnr.: **WO2008027839**

(30) Prioritet: **2006-08-31 US 824197 P**

(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 MT NL PL PT RO SE SI SK TR**

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(54) Benævnelse: **Sensibilisering af tumorceller til strålebehandling ved indgivelse af agonister til endothelin**

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DESCRIPTION

FIELD OF THE INVENTION

[0001] The present invention relates to the sensitization of tumor cells to radiation therapy through the administration of endothelin Type B (ET_B) receptor agonists. More specifically, the present invention relates to the sensitization of tumor cells to radiation therapy through the administration of IRL1620 (N-suc-[Glu^9, $Ala^{11,15}$] ET-1 (8-21)).

BACKGROUND OF THE INVENTION

[0002] Radiation therapy (irradiation) is an effective modality for the treatment of a variety of tumor types. Half of all cancer patients will receive radiation therapy during their course of treatment for cancer. Therefore, advances that increase the efficacy of radiation therapy would provide a great benefit. The present invention provides such an advance.

SUMMARY OF THE INVENTION

[0003] The present invention provides for the sensitization of tumor cells to radiation therapy through the administration of an endothelin agonist. Endothelin agonists provide this benefit by selectively increasing blood supply (and resulting oxygenation) to tumors thereby sensitizing the tumor cells to radiation therapy. Endothelin agonists can selectively increase blood flow to tumor cells through these compounds' interaction with the specialized vasculature of tumor tissue.

[0004] Specifically, one embodiment according to the present invention includes an article of manufacture comprising a composition comprising an ET_B agonist, and instructional information directing the administration of said composition with a radiation therapy, for use in sensitization of tumor cells to radiation characterized in that said ET_B receptor agonist is IRL1620.

[0005] The invention further provides a composition for use in the treatment of a tumor comprising an ET_B agonist wherein said composition is directed to be administered in conjunction with a radiation therapy, characterized in that said ET_B agonist is IRL1620.

[0006] In certain embodiments, the endothelin agonist is administered to a patient in need thereof wherein the administering comprises systemic and/or local administration and the patient will receive at least two radiation therapies. In this embodiment, the administering of the endothelin agonist occurs in a manner selected from the group consisting of before all radiation therapies of the patient; before a subset of the radiation therapies of the patient; after all radiation therapies of the patient; after a subset of the radiation therapies of the patient; before and after all the radiation therapies of the patient; before all radiation therapies of the patient and after a subset of the radiation therapies of the patient; before a subset of the radiation therapies of the patient and after all radiation therapies of the patient; and before a subset of the radiation therapies of the patient and after a subset of the radiation therapies of the patient.

[0007] Endothelin agonists can be administered systemically and/or locally. Appropriate administration routes can include, without limitation, oral administration, intra-tumoral administration, intravenous administration, intravesical administration, intraarterial administration, intranasal administration and combinations thereof.

[0008] The applicants have developed a radiation combination therapy wherein a first radiation sensitizing compound and a second radiation sensitizing compound are co-administered and wherein the first radiation sensitizing compound enhances the effectiveness (increasing the sensitivity of a tumor cell to the cytototxic effects of radiation) of the second radiation sensitizer. Such embodiments include, the ET_B receptor agonist IRL1620.

[0009] In another embodiment of the present invention the first and said second radiation sensitizers are synergistic and/or additive in their effects such that both the first and the second radiation sensitizer are more effective in sensitizing a tumor to the cytotoxic effects of radiation therapy than either first and said second radiation sensitizer used alone.

[0010] Embodiments according to the present invention also include a composition for use in the treatment of cancer comprising

an ET_B agonist wherein said composition is directed to be administered in conjunction with a radiation therapy, characterized in that said ET_B agonist is IRL1620.

[0011] Cancers treated in accordance with the present invention can include solid tumor or lymphomas. In certain embodiments, the treated cancer can include one or more of an ovarian tumor, a colon tumor, Kaposi's sarcoma, a breast tumor, a melanoma, a prostate tumor, a meningioma, a liver tumor, a breast phyllode tumor and combinations thereof.

BRIEF DESCRIPTION OF THE FIGURES

[0012] FIG. 1 shows the effect of the ET_B agonist IRL1620 on the reduction in tumor volume induced by radiation therapy.

DETAILED DESCRIPTION

I. Definitions

[0013] Instructional Information: As used herein, the term "instructional information" shall mean material accompanying a pharmaceutical product that provides a description of how to administer the product. This instructional information generally is regarded as the "label" for a pharmaceutical product. Instructional information can come in many forms including, without limitation, a paper insert, c.d. rom or directions to a web site containing information relating to the pharmaceutical product.

[0014] Prodrug: As used herein, the term "prodrug" shall mean compounds that transform rapidly in vivo to a compound useful in the invention, for example, by hydrolysis. A thorough discussion of prodrugs is provided in Higuchi et al., Prodrugs as Novel Delivery Systems, Vol. 14, of the A.C.S.D. Symposium Series, and in Roche (ed.), Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987.

[0015] Radiation Therapies: As used herein, the phrase "radiation therapies" shall mean radiation treatments administered to a patient that are separated by a period of time. The period of time separating the radiation therapies can be determined by a treating physician or veterinarian and can include, without limitation, minutes, hours, days, weeks, months or years. A given radiation therapy can be the same as or different from the radiation therapy immediately preceding or following it.

[0016] Sensitize and Sensitizing: As used herein, the terms "sensitize" or "sensitizing" shall mean making a tumor more susceptible to a treatment.

[0017] Treat, Treatment and Contributing to the Treatment Of: As used herein, the terms "treat", "treatment" and "contributing to the treatment of" shall mean preventing, retarding the progression or growth of, shrinking, or eliminating a cancer including a solid tumor or lymphoma. As such, these terms include both medical therapeutic and/or prophylactic administration, as appropriate.

[0018] The angioarchitecture of tumor blood vessels is different from that of normal blood vessels. Carmeliet & Jain, Nature, 407:249 (2000). Therefore, the vascular reactivity of tumors differs from that of normal tissue. For example, the administration of nitric oxide donors, nicotinamide and bradykinin agonists modulate blood flow to tumors. Jordan et al., Int J Radiat Oncol Biol Phys, 48:565 (2000); Fukumura et al., Am J Pathol, 150:713 (1997); Hirst et al., Br J Radiol, 67: 795 (1994). The present invention relates to the discovery that the unique angioarchitecture of tumor blood vessels allows endothelin agonists including ET_B agonists to selectively increase blood supply to tumors and thereby sensitize the tumors to radiation therapy.

[0019] Endothelin is a vasoactive substance that modulates blood flow and is present in large concentrations in breast carcinoma tissues compared to normal breast tissue (specifically, endothelin can be present in an amount of about 12 pg/mg in breast carcinoma tissues as compared to about 0.12 pg/mg in normal breast tissue). Kojima et al., Surg Oncol, 4(6):309 (1995); Kurbel et al., Med Hypotheses, 52(4):329 (1999); Patel et al., Mol Cell Endocrinol, 126(2):143 (1997); Yamashita et al., Cancer Res, 52(14):4046 (1992); Yamashita et al., Res Commun Chem Pathol Pharmacol, 74(3):363 (1991). Endothelins are a family of cyclic peptides with 21 amino acids, comprising three isoforms in mammals, ET-1, ET-2 and ET-3. Inoue et al., Proc Natl Acad Sci USA 86:2863 (1989); Yanagisawa et al., Nature, 332:411 (1988). Endothelins exert their effects by binding to two distinct cell surface receptors, ET_A and ET_B. The ET_B receptor binds the three peptide isotypes with equal affinity. In contrast, the ET_A receptor binds ET-1 with higher affinity than the other isoforms. Both receptors belong to the G protein-coupled receptor system

and mediate biological responses from a variety of stimuli, including growth factors, vasoactive polypeptides, neurotransmitters and hormones. Masaki, J Cardiovasc Pharmacol, 35:S3 (2000); Gulati, Preface. Adv Drug Deliv Rev, 40:129 (2000); Gulati et al., Am J Physiol, 273:H827 (1997); Levin, N Engl J Med, 333:356 (1995). ET_B receptors, a focus of the present invention, are present on both endothelial cells (ECs) and vascular smooth muscle cells (VSMCs) and are increased in breast cancer tissue (including in invasive as well as in ductal and lobular breast carcinoma tissue in humans) when compared to normal breast tissue. Wulfing et al., Oncol Rep, 11:791 (2004); Wulfing et al., Clin Cancer Res, 9:4125 (2003); Alanen et al., Histopathology, 36(2):161 (2000). Endothelin acts on ET_B receptors to produce vascular dilation and increase blood flow to breast tumor tissue. ET_B receptors predominating on ECs, produce vasodilatation via the release of factors such as prostacyclin and nitric oxide. de Nucci et al., Proc Natl Acad Sci USA, 85:9797 (1988). Because ET-1 produces an increase in blood flow to tumors by stimulating ET_B receptors, an ET_B receptor agonist can be used to selectively increase blood supply to tumors, thus increasing oxygenation of the tumors and sensitizing them to the effects of radiation therapy.

[0020] ET_B receptors have been shown in, for example and without limitation, ovarian cancers, myofibroblasts, Kaposi's sarcoma tumor and intratumoral vessels, breast cancers and melanomas. Bagnato et al., Am J Pathol, 158:841 (2001); Alanen et al., Histopathology, 36(2):161 (2000); Bagnato et al., Cancer Res, 59:720 (1999); Kikuchi et al., Biochem Biophys Res Comm, 219:734 (1996). Therefore, administration of an ET_B receptor agonist in combination with a radiation therapy can be used to contribute to the treatment of solid tumor or lymphomas, including, without limitation, ovarian cancer, colon carcinoma, Kapoli's sarcoma, breast cancer, and melanomas.

[0021] The ET_B agonists useful in accordance with the present invention is IRL1620. IRL1620 is a truncated linear synthetic analogs of ET-1 and is one of the most widely used selective synthetic agonists. IRL1620 is a linear ET-analog whose structure is based on the carboxy terminal end of ET-1 and has 120,000 fold selectivity for the ET_B receptors. Okada & Nishikibe, Cardiovasc Drug Rev, 20:53 (2002); Douglas et al., Br J Pharmacol, 114:1529 (1995). IRL1620 is a highly selective and potent ET_B agonist, with evidence being reported of its selectivity for the ET_{B1} receptor subtype in preference over the ET_{B2} subtype. Brooks et al., J Cardiovasc Pharmacol, 26 Suppl 3:S322 (1995).

[0022] In one embodiment of the present invention, an endothelin agonist is used in conjunction with a radiation therapy to contribute to the treatment of a solid tumor or lymphoma. In this method, the endothelin agonist, notably an ET_B agonist, increases blood flow to the tumor, which is rich in ET_B receptors.

[0023] As previously suggested, it is theorized, but not relied upon herein, that endothelin agonists stimulate ET_B receptors to dilate tumor blood vessels, thereby increasing blood flow to the tumor. The increased blood perfusion of tumors caused by ET_B agonists increases oxygenation of the tissue, enhancing the therapeutic action of radiation therapies.

Example 1. Effect of IRL1620 on Tumor Radiation Therapy

[0024] As shown in the previously described example, endothelin selectively and transitionally increases blood flow to tumors producing increased oxygenation of the tumor. As oxygenation increases, so can radiation-induced cellular damage. Thus, the following described study was conducted to determine if IRL1620, an ETB agonist can increase the sensitivity of tumors to radiation therapy.

[0025] Inbred male Swiss albino mice (25 g) were used as subjects. Tumors were induced with Dalton's Lymphoma Ascites cells (1 million cells per animal). After 30 days, tumor volume was determined and animals with tumor sizes of about 1 cm^3 or greater were included in the study. Animals were divided into six groups (10 animals per group) and were treated as described below every other day for five doses:

Group I:

No treatment

Group II:

5 doses of saline on every alternate day via the tail vein plus radiation (4 Gy/dose) given 15 minutes after each dose of saline;

Group III:

5 doses of IRL1620 (9 nmol/kg) on every alternate day via the tail vein plus radiation (4 Gy/dose) given 15 minutes after each dose of IRL1620;

Group IV:

5 doses of IRL1620 (3 nmol/kg) on every alternate day via the tail vein plus radiation (4 Gy/dose) given 15 minutes after each dose of IRL1620;

Group V:

5 doses of IRL1620 (1 nmol/kg) on every alternate day via the tail vein plus radiation (4 Gy/dose) given 15 minutes after each dose of IRL1620; and

Group VI:

5 doses of IRL1620 (9 nmol/kg) on every alternate day via the tail vein.

[0026] During radiation mice were shielded with lead except for a 3 cm diameter circular field where the tumor was centered. Tumor volume measurements occurred on days 40, 43, 46, 49, 52, 55, 58, 61, 64, 67 and 70 after tumor induction. Tumor diameter was measured using a digital caliper and tumor volume was calculated using the formula:

$$V = \Pi r_1^2 r_2$$

where r_1 and r_2 are two perpendicular radii at the widest and longest regions of the tumor.

Survival of the animals was also documented.

[0027] As can be seen in Fig. 1,there was a significant increase in tumor volume in control animals and all control animals died by 53 days after tumor induction. Radiation alone did not significantly reduce tumor volume when compared to controls and there was no significant increase in survival. All radiation alone animals died by 56 days after tumor induction.

[0028] Animals treated with radiation 15 minutes after administration of 9 nmol/kg IRL1620 showed a significant reduction in tumor volume with a significant increase in life span. Only 4 out of 10 animals in this group died by 70 days after tumor induction. Animals treated with 9 nmol/kg IRL1620 alone produced a decrease in the development of tumor volume initially even though it was not as significant as animals treated with radiation 15 minutes after administration of 9 nmol/kg IRL1620. It was found that in this group 6 out of 10 animals died by 70 days after tumor induction. Animals treated with radiation 15 minutes after administration of 3 nmol/kg IRL1620 delayed the development of tumors. It was found that 7 out of 10 animals died by 70 days after tumor induction. Animals treated with radiation 15 minutes after administration of 1 nmol/kg IRL1620 along with radiation delayed tumor development. It was found that in this group 9 out of 10 animals died by 70 days after tumor induction. This study demonstrates that ET_B agonists such as IRL1620 can be used as tumor radiation sensitizers.

[0029] In conclusion, endothelin agonists including the ET_B agonist IRL1620 can be used as tumor-selective vasodilators and can be used to increase the efficacy of radiation therapy.

[0030] Pharmaceutical compositions containing the active ingredients are suitable for administration to humans or other mammals. Typically, the pharmaceutical compositions are sterile, and contain no toxic, carcinogenic, or mutagenic compounds that would cause an adverse reaction when administered. Administration of the pharmaceutical composition can be performed before, during, or after the onset of solid tumor or lymphoma growth.

[0031] A method of the present invention can be accomplished using active ingredients as described above, or as a physiologically acceptable salt, derivative, prodrug, or solvate thereof. The active ingredients can be administered as the neat compound, or as a pharmaceutical composition containing either or both entities.

[0032] The pharmaceutical compositions include those wherein the active ingredients are administered in an effective amount to achieve their intended purpose. More specifically, a "therapeutically effective amount" means an amount effective to prevent development of, to eliminate, to retard the progression of, or to reduce the size of a solid tumor or lymphoma. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[0033] A "therapeutically effective dose" refers to that amount of the active ingredients that results in achieving the desired effect. Toxicity and therapeutic efficacy of such active ingredients can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index, which is expressed as the ratio between LD_{50} and ED_{50}. A high therapeutic index is preferred. The data obtained can be used in formulating a range of dosage for use in humans. The dosage of the active ingredients preferably lies within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage can vary within this range depending upon

the dosage form employed, and the route of administration utilized.

[0034] The exact formulation and dosage is determined by an individual physician in view of the patient's condition. Dosage amount and interval can be adjusted individually to provide levels of the active ingredients that are sufficient to maintain therapeutic or prophylactic effects.

[0035] The amount of pharmaceutical composition administered can be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration, and the judgment of the prescribing physician.

[0036] The active ingredients can be administered alone, or in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. Pharmaceutical compositions for use in accordance with the present invention thus can be formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries that facilitate processing of the active ingredients into preparations which can be used pharmaceutically.

[0037] When a therapeutically effective amount of the active ingredients is administered, the composition can be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred composition for intravenous injection typically will contain an isotonic vehicle although this characteristic is not required.

[0038] For veterinary use, the active ingredients are administered as a suitably acceptable formulation in accordance with normal veterinary practice. The veterinarian can readily determine the dosing regimen that is most appropriate for a particular animal.

[0039] Administration routes can include systemic or local routes and can include, without limitation, oral administration, intra-tumoral administration, intravenous administration, intravesical administration, intraarterial administration, intranasal administration, and combinations thereof.

[0040] In certain embodiments, the endothelin agonist is administered to a patient in need thereof wherein the administering comprises systemic and/or local administration and the patient will receive at least two radiation therapies. In this embodiment, the administering of the endothelin agonist occurs in a manner selected from the group consisting of before all radiation therapies of the patient; before a subset of the radiation therapies of the patient; after all radiation therapies of the patient; after a subset of the radiation therapies of the patient; before and after all the radiation therapies of the patient; before all radiation therapies of the patient and after a subset of the radiation therapies of the patient; before a subset of the radiation therapies of the patient and after all radiation therapies of the patient; and before a subset of the radiation therapies of the patient and after a subset of the radiation therapies of the patient.

[0041] Radiation dosages and schedules used in accordance with the present invention can vary depending on the organ to be treated. Generally, appropriate dosages will range from about 1 to about 300 grey/dose. Total dosages can vary from about 200 to about 5000 grey. Schedules used in accordance with the present invention can also vary. In certain embodiments, a particular schedule can comprise daily treatments about 5 times per week for about six to about seven weeks or can comprise about twice daily treatments for about two to about three weeks. Particular dosages and schedules, however, will vary depending on the needs of particular patients and these provided examples should not be read as limiting the scope of the present invention. Finally, it should be noted that endothelin agonists including, without limitation, IRL1620, can also be used to enhance radiation enhancers. When used in this capacity, the endothelin agonists and radiation therapies can be administered according to all treatment embodiments previously described herein as if individually described.

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

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Patentkrav

1. Et produkt omfattende en sammensætning omfattende en endothelin type B ET_B receptoragonist, og instruerende information til indgivelse af sammensætningen, til anvendelse sammen med en strålebehandling af en tumor, **kendetegnet ved, at** ET_B receptoragonisten er IRL1620 (N-suc-[Glu^9, $Ala^{11,15}$] ET-1 (8-21)).

2. Sammensætning til anvendelse i behandlingen af en tumor, omfattende en ET_B receptoragonist, hvor sammensætningen er rettet mod indgivelse i forbindelse med en strålebehandling, **kendetegnet ved, at** ET_B receptoragonisten er IRL1620.

3. Sammensætning til anvendelse ifølge krav 2, hvor sammensætningen er rettet mod systemisk og / eller lokal indgivelse.

4. Sammensætning til anvendelse ifølge krav 2, hvor sammensætningen er rettet mod en indgivelse valgt blandt en eller flere fra gruppen bestående af oral indgivelse, intratumoral indgivelse, intravenøs indgivelse, intravesikal indgivelse, intraarteriel indgivelse, intranasal indgivelse, og kombinationer deraf.

5. Sammensætning til anvendelse ifølge krav 2, hvor sammensætningen er rettet mod en indgivelse valgt fra gruppen bestående af før alle strålebehandlinger af en patient; før en delmængde af strålebehandlinger af en patient; efter alle strålebehandlinger af en patient; efter en delmængde af strålebehandlinger af en patient; før og efter alle

strålebehandlinger af en patient; før alle strålebehandlinger af en patient og efter en delmængde af strålebehandlinger af en patient; før en delmængde af strålebehandlinger af en patient og efter alle strålebehandlinger af en patient; og før en delmængde af strålebehandlinger af en patient og efter en delmængde af strålebehandlinger af en patient.

6. Sammensætning til anvendelse i behandlingen af cancer omfattende en ET_B receptoragonist, hvor sammensætningen er rettet mod indgivelse i forbindelse med en strålebehandling, **kendetegnet ved, at** ET_B agonisten er IRL1620.

DRAWINGS

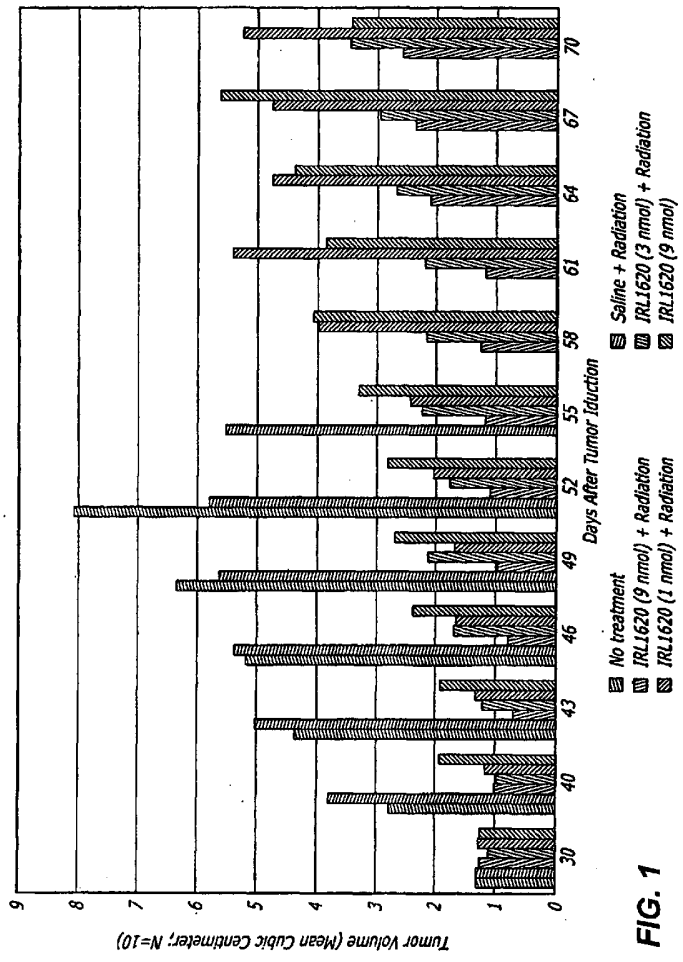

FIG. 1