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(54) **METHODS AND COMPOSITIONS FOR TREATING CANCER**

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USPC 514/170, 182
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(57) **ABSTRACT**

Methods and compositions for treating cancer are described herein. More particularly, the methods for treating cancer comprise administering a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor, such as abiraterone acetate (i.e., 3β-acetoxy-17-(3-pyridyl)androsta-5,16-diene), in combination with at least one additional therapeutic agent such as an anti-cancer agent or a steroid. Furthermore, disclosed are compositions comprising a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor, and at least one additional therapeutic agent, such as an anti-cancer agent or a steroid.

20 Claims, No Drawings

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METHODS AND COMPOSITIONS FOR TREATING CANCER

FIELD OF THE INVENTION

Methods and compositions for treating cancer are described herein. More particularly, the methods for treating cancer comprise administering a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor, such as abiraterone acetate (i.e., 3β-acetoxy-17-(3-pyridyl) androsta-5,16-diene), in combination with at least one additional therapeutic agent, such as an anti-cancer agent or a steroid. Furthermore, disclosed are compositions comprising a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor, and at least one additional therapeutic agent such as an anti-cancer agent or a steroid, e.g., a corticosteroid or, more specifically, a glucocorticoid.

BACKGROUND

The number of people diagnosed with cancer has significantly increased. Of special interest are individuals diagnosed with androgen-dependent disorders, such as prostate cancer, and estrogen-dependent disorders, such as breast cancer since such diagnoses are increasing in number at an alarming rate.

Prostate cancer is currently the most common non-skin cancer and the second leading cause of cancer-related death in men after lung cancer. The primary course of treatment for patients diagnosed with organ-confined prostate cancer is usually prostatectomy or radiotherapy. Not only are these treatments highly invasive and have undesirable side effects, such localized treatments are not effective on prostate cancer after it has metastasized. Moreover, a large percent of individuals who receive localized treatments will suffer from recurring cancer.

Additionally, breast cancer incidence in women has increased from one out of every 20 women in 1960 to one out of every eight women in 2005. Moreover, it is the most common cancer among white and African-American women. Similar to treating prostate cancer, most options for women diagnosed with breast cancer are highly invasive and have significant side-effects. Such treatments include surgery, radiation and chemotherapy.

Hormone therapy is another treatment option for individuals diagnosed with prostate or breast cancer. Hormone therapy is a form of systemic treatment for prostate or breast cancer wherein hormone ablation agents are used to suppress the production or block the effects of hormones, such as estrogen and progesterone in the body, which are believed to promote the growth of breast cancer, as well as testosterone and dihydrotestosterone, which are believed to promote the growth of prostate cancer. Moreover, hormone therapy is less invasive than surgery and does not have many of the side effects associated with chemotherapy or radiation. Hormone therapy can also be used by itself or in addition to localized therapy and has shown to be effective in individuals whose cancer has metastasized.

Even though hormone therapy is less invasive and can be used on more advanced stages of cancer, some individuals administered current hormone therapy treatments may not show a significant response or may not show any response at all to such treatments. Additionally, some patients treated with current hormone therapy treatments may also suffer from relapsing or recurring cancer. Currently, such refractory cancer patients are left with very few treatment options.

Despite the progress made in the treatment of cancer, there

tionally, there is a need for effective anti-cancer treatment options for patients who are not responding to current anti-cancer treatments. Also, there is a need for effective anti-cancer treatment options for patients whose cancer has recurred.

SUMMARY OF THE INVENTION

Described herein are methods for treating a cancer in which a therapeutically effective amount of a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor, such as abiraterone acetate (i.e. 3β-acetoxy-17-(3-pyridyl)androsta-5,16-diene), is administered to a patient, e.g., a patient in need thereof, in combination with a therapeutically effective amount of at least one additional therapeutic agent including, but not limited to, an anti-cancer agent or steroid. Such methods can also provide an effective treatment for individuals with a refractory cancer, including individuals who are currently undergoing a cancer treatment. Therefore, in certain embodiments, the method is directed to treating a refractory cancer in a patient, in which a therapeutically effective amount of 17α-hydroxylase/$C_{17,20}$-lyase inhibitor is administered to a patient currently receiving an anti-cancer agent.

For example, in certain embodiments, the method for the treatment of a cancer in a mammal comprises administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 0.1 mg/m^2 to about 20 mg/m^2 of mitoxantrone.

In another embodiment, the method for the treatment of a cancer in a mammal comprises administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 1 mg/m^2 to about 175 mg/m^2 of paclitaxel.

In still other embodiments, the method for the treatment of a cancer in a mammal comprises administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 1 mg/m^2 to about 100 mg/m^2 of docetaxel.

Furthermore, described herein is a method for the treatment of a cancer in a mammal comprising administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate; and an amount of about 0.01 mg to about 200 mg of leuprolide, wherein the leuprolide is administered over a period of about 3 days to about 12 months.

In other embodiments, the method for the treatment of a cancer in a mammal comprises administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 0.01 mg to about 20 mg of goserelin, wherein the goserelin is administered over a period of about 28 days to about 3 months.

Additionally, in another embodiment, the method for the treatment of a cancer in a mammal comprises administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 0.01 mg to about 20 mg of triptorelin, wherein the triptorelin is administered over a period of about 1 month.

The method for the treatment of a cancer in a mammal can also comprise administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 0.1 μg/day to about 500 μg/day of seocalcitol, such as about 100 μg/day of seocalcitol.

Also, the method for the treatment of a cancer in a mammal can comprise administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an

In yet another embodiment, the method for the treatment of a cancer in a mammal can comprise administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 1 mg/day to about 2000 mg/day of flutamide.

Moreover, the method for the treatment of a cancer in a mammal can comprise administering an amount of about 50 mg/day to about 2000 mg/day of abiraterone acetate and an amount of about 0.01 mg/day to about 500 mg/day of a glucocorticoid including, but not limited to, hydrocortisone, prednisone or dexamethasone.

Also described herein are compositions for the treatment of cancer that comprise a combination of a therapeutically effective amount of at least one 17α-hydroxylase/$C_{17,20}$-lyase inhibitor and a therapeutically effective amount of at least one additional anti-cancer agent, such as, but not limited to, mitoxantrone, paclitaxel, docetaxel, leuprolide, goserelin, triptorelin, seocalcitol, bicalutamide, flutamide, or a steroid including, but not limited to, hydrocortisone, prednisone, or dexamethasone.

Finally, single unit dosage forms comprising abiraterone acetate and a glucocorticoid, optionally with carriers, diluents or excipients, are contemplated. Also, kits comprising at least one 17α-hydroxylase/$C_{17,20}$-lyase inhibitor and an additional anti cancer agent or steroid are contemplated. For example, the kit may include a vial containing abiraterone acetate and another vial containing a glucocorticoid.

DEFINITIONS

As used herein and unless otherwise defined the word "cancer," refers to the growth, division or proliferation of abnormal cells in the body. Cancers that can be treated with the methods and the compositions described herein include, but are not limited to, prostate cancer, breast cancer, adrenal cancer, leukemia, lymphoma, myeloma, Waldenström's macroglobulinemia, monoclonal gammopathy, benign monoclonal gammopathy, heavy chain disease, bone and connective tissue sarcoma, brain tumors, thyroid cancer, pancreatic cancer, pituitary cancer, eye cancer, vaginal cancer, vulvar cancer, cervical cancer, uterine cancer, ovarian cancer, esophageal cancer, stomach cancer, colon cancer, rectal cancer, liver cancer, gallbladder cancer, cholangiocarcinoma, lung cancer, testicular cancer, penal cancer, oral cancer, skin cancer, kidney cancers, Wilms' tumor and bladder cancer.

As used herein, and unless otherwise defined, the terms "treat," "treating" and "treatment" include the eradication, removal, modification, management or control of a tumor or primary, regional, or metastatic cancer cells or tissue and the minimization or delay of the spread of cancer.

As used herein, and unless otherwise defined, the term "patient" means an animal, including but not limited to an animal such as a human, monkey, cow, horse, sheep, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit, or guinea pig. In one embodiment, the patient is a mammal and in another embodiment the patient is a human. In certain embodiments, the patient can be an adult male or female. In some embodiments, the patient is a male of age about 30 years to about 85 years. In other embodiments, the patient is a female of age about 30 years to about 85 years. In a particular embodiment, the patient has or is susceptible to having (e.g., through genetic or environmental factors) cancer. In a further embodiment, the patient has or is susceptible to having (e.g., through genetic or environmental factors) a tumor. In other embodiments, the patient can be castrated or non-castrated.

lyase, (which is an enzyme in testosterone synthesis), an analog thereof, derivative thereof, metabolite thereof or pharmaceutically acceptable salt thereof. Also, unless otherwise noted, reference to a particular 17α-hydroxylase/$C_{17,20}$-lyase inhibitor can include analogs, derivatives, metabolites or pharmaceutically acceptable salts of such particular 17α-hydroxylase/$C_{17,20}$-lyase inhibitor.

The term "anti-cancer agent" as used herein refers to any therapeutic agent that directly or indirectly kills cancer cells or directly or indirectly prohibits stops or reduces the proliferation of cancer cells. It should be noted that even though throughout this specification and in the claims the phrase "anti-cancer agent" is written as a singular noun, for example; "an anti-cancer agent" or "the anti-cancer agent," the phrase "anti-cancer agent" should not be interpreted as being limited to the inclusion of a single anti-cancer agent.

As used herein, and unless otherwise defined, the phrase "therapeutically effective amount" when used in connection with a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor or therapeutic agent means an amount of the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor or therapeutic agent effective for treating a disease or disorder disclosed herein, such as cancer.

As used herein and unless otherwise defined the phrase "refractory cancer," means cancer that is not responding to an anti-cancer treatment or cancer that is not responding sufficiently to an anti-cancer treatment. Refractory cancer can also include recurring or relapsing cancer.

As used herein and unless otherwise defined the phrase "refractory patient," means a patient who has refractory cancer.

As used herein and unless otherwise defined the phrase "relapse cancer," means cancer that was at one time responsive to an anti-cancer treatment but has become no longer responsive to such treatment or is no longer responding sufficiently to such treatment.

As used herein and unless otherwise defined the phrase "recurring cancer," means cancer that has returned after a patient has been earlier diagnosed with cancer, under gone treatment or had been previously diagnosed as cancer-free.

As used herein and unless otherwise defined the term "derivative" refers to a chemically modified compound wherein the chemical modification takes place at one or more functional groups of the compound. The derivative may retain or improve the pharmacological activity of the compound from which it is derived.

As used herein and unless otherwise defined the term "analog" refers to a chemical compound that is structurally similar to another but differs slightly in composition (as in the replacement of one atom by an atom of a different element or in the presence of a particular functional group).

As used herein and unless otherwise defined the phrase "pharmaceutically acceptable salt" refers to any salt of a 17α-hydroxylase/$C_{17,20}$-lyase inhibitor which retains the biological effectiveness of the 17α-hydroxylase/$C_{17,20}$-lyase inhibitor. Examples of pharmaceutically acceptable salts include, but are not limited to, acetates, sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sul-

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