Methods for treating lung disorders

Cross Reference

This application claims priority to U.S. Provisional Patent Application Serial Nos. 62/519257 filed June 14, 2017; 62/628582 filed February 9, 2018; 62/653942 filed April 6, 2018; and 62/678387 filed May 31, 2018, each incorporated by reference herein in their entirety.

Background

Lung cancer is the second most common cancer and one of the most lethal. Conventional therapies such as surgical resection, radiation, and chemotherapy have not resulted in satisfactory long-term survival rates. Systemic drug delivery, even at a high dose, results in only a limited amount of taxane drugs reaching lung tumors. Improved methods for treating lung tumors are thus needed.

Summary

In one aspect, the present disclosure refers to the use of a composition in the manufacture of a medicament for treating a lung tumor, wherein the use comprises that an amount effective of the composition comprising taxane particles to treat the lung tumor is to be pulmonary administered to the subject, wherein the taxane particles comprise at least 95% of the taxane and have a mean particle size (number) of between 0.1 μm and 5 μm, wherein the taxane particles have a specific surface area (SSA) of at least 12 m2/g, wherein the taxane particles are present in a suspension comprising the taxane particles and a pharmaceutically acceptable carrier, wherein the suspension is aerosolized for administration, wherein the pulmonary administration comprises nebulization, and wherein the nebulization results in pulmonary delivery to the subject of aerosol droplets of the taxane particles suspension.

In one example, the disclosure provides methods for treating a lung disorder, such as a lung tumor or pulmonary fibrosis, comprising pulmonary administration to a subject with a lung disorder of an amount effective of a composition comprising taxane particles to treat the lung disorder, wherein the taxane particles comprise at least 95% of the taxane and have a mean particle size (number) of between 0.1 μm and 5 μm. In one example, the pulmonary administration may comprise nebulization, wherein the nebulizing results in pulmonary

delivery to the subject of aerosol droplets of the taxane particles or suspension thereof. In another example, the taxane particles may have a mean particle size (number) of between 0.4 μm and 2 μm. In further examples, the taxane particles may have a mean particle size (number) of between about 0.4 μm and about 1.2 μm, or between about 0.6 μm and about 1.0 μm.

In another example, the taxane particles may have a specific surface area (SSA) of at least 10 m^2/g, or at least 12 m^2/g, 14 m^2/g, 16 m^2/g, 18 m^2/g, 20 m^2/g, 25 m^2/g, 30 m^2/g, 32 m^2/g, 34 m^2/g, or 35 m^2/g; or wherein the taxane particles have an SSA of between about 10 m^2/g and about 60 m^2/g. In another example, the taxane particles may be present in a suspension, wherein the suspension comprises:

(a) the taxane particles;

(b) a pharmaceutically acceptable carrier; and

(c) a polysorbate, wherein the polysorbate is present in the suspension at a concentration of between about 0.01% v/v and about 1.5% v/v, or between about 0.01% v/v and about 1% v/v, about 0.01% v/v and about 0.5% v/v, about 0.01% v/v and about 0.4% v/v, about 0.01% v/v and about 0.25% v/v, about 0.05% v/v and about 0.5% v/v, about 0.05% v/v and about 0.25% v/v, about 0.1% v/v and about 0.5% v/v, about 0.1% v/v and about 0.25% v/v, about 0.1% v/v, about 0.16 v/v, or about 0.25% v/v. In one example, the pharmaceutically acceptable carrier may be saline, such as 0.9% sodium chloride solution. In another example, the polysorbate may be polysorbate 80. In a further example, the taxane may be present in the suspension at a concentration between about 1 mg/ml and about 40 mg/ml, or about 6 mg/ml and about 20 mg/ml.

In another example, the taxane particles and suspensions thereof may be uncoated and exclude lipids, polymers, proteins such as albumin, polyethoxylated castor oil, and/or polyethylene glycol glycerides composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol.

In other examples, the taxane may comprise paclitaxel, docetaxel, cabazitaxel, or a pharmaceutically acceptable salt thereof. In one example, the taxane may comprise paclitaxel or a pharmaceutically acceptable salt thereof; in this example, the particles may have one or more of the following characteristics:

(a) a mean bulk density (not tapped) between about 0.050 g/cm^3 and about 0.12 g/cm^3, or between about 0.060 g/cm^3 and about 0.11 g/cm^3;

(b) a SSA of at least 12 m^2/g, 15 m^2/g, 18 m^2/g, 20 m^2/g, 25 m^2/g, 30 m^2/g, 32 m^2/g, 34 m^2/g, or 35 m^2/g;

(c) a SSA of between about 22 m^2/g and about 40 m^2/g, 25 m^2/g and about 40 m^2/g, 30 m^2/g and about 40 m^2/g, or between about 35 m^2/g and about 40 m^2/g; and/or

(d) wherein at least 40% (w/w) of the paclitaxel is dissolved in 30 minutes or less in a solution of 50% methanol /50% water (v/v) at 37°C and pH 7.0 in a USP II paddle apparatus operating at 75 RPM.

In another example, the taxane particles may comprise docetaxel or a pharmaceutically acceptable salt thereof; in this example, the particles may have one or more of the following characteristics:

(a) a mean bulk density (not tapped) between about 0.050 g/cm^3 and about 0.12 g/cm^3, or between about 0.06 g/cm^3 and about 0.1 g/cm^3;

(b) a SSA of at least 12 m^2/g, 15 m^2/g, 18 m^2/g, 20 m^2/g, 25 m^2/g, 30 m^2/g, 35 m^2/g, 40 m^2/g, or 42 m^2/g;

(c) a SSA of between about 20 m^2/g and about 50 m^2/g, or between about 35 m^2/g and about 46 m^2/g; and/or

(d) wherein at least 20% (w/w) of the docetaxel is dissolved in 30 minutes or less in a solution of 15% methanol /85% water (v/v) at 37°C and pH 7.0 in a USP II paddle apparatus operating at 75 RPM.

In another example, the taxane particles may be in crystalline form. In a further example, the taxane particles or suspensions thereof are aerosolized for administration, and the aerosol droplets have a mass median aerodynamic diameter (MMAD) of between about 0.5 μm to about 6 μm diameter, or between about 1 μm to about 3 μm diameter, or about 2 μm to about 3 μm diameter.

In one example, the taxane may remain detectable in lung tissue of the subject for at least 4 days after the administering.

In some examples, the taxane particles reside at the tumor site after administration of the composition exposing the tumor to the taxane particles for a sustained amount of time sufficient to stimulate the endogenous immune system of the subject resulting in the production of tumoricidal cells and infiltration of the tumoricidal cells into the tumor at a level sufficient to treat the tumor. In some examples, the stimulation of the endogenous immune systems produces a cellular (cell-mediated) immune response. In other examples, the stimulation of the endogenous immune system produces a humoral immune response. In

some examples, the stimulation of the endogenous immune system produces a tumor vaccine. In some examples, metastases are reduced or eliminated.

In one example, the sustained amount of time is at least 4 weeks.

In some examples, the tumoricidal cells comprise T-cells, B cells, or natural killer (NK) cells, or combinations thereof.

In some examples, the composition is administered in two or more separate administrations.

In some examples, the two or more separate administrations are administered once a week for at least two weeks.

In other examples, the two or more separate administrations are administered twice a week for at least one week, wherein the two or more separate administrations are separated by at least one day.

In some examples, the treatment of the tumor is elimination of the tumor.

Disclosed in the context of the present disclosure are the following examples 1 to 25:

Example 1 is a method for treating a lung disorder, including but not limited to a lung tumor or pulmonary fibrosis, comprising pulmonary administration to a subject with a lung disorder of an amount effective of a composition comprising taxane particles to treat the lung disorder, wherein the taxane particles comprise at least 95% of the taxane and have a mean particle size (number) of between 0.1 μm and 5 μm.

Example 2 is the method of example 1, wherein the pulmonary administration comprises nebulization, and wherein the nebulizing results in pulmonary delivery to the subject of aerosol droplets of the taxane particles or suspension thereof.

Example 3 is the method of any one of examples 1-2, wherein the taxane particles have a mean particle size (number) of between 0.4 μm and 2 μm.

Example 4 is the method of any one of examples 1-3, wherein the taxane particles have a mean particle size (number) of between about 0.4 μm and about 1.2 μm, or between about 0.6 μm and about 1.0 μm.

Example 5 is the method of any one of examples 1-4, wherein the taxane particles have a specific surface area (SSA) of at least 10 m^2/g, or at least 12 m^2/g, 14 m^2/g, 16 m^2/g, 18 m^2/g, 20 m^2/g, 25 m^2/g, 30 m^2/g, 32 m^2/g, 34 m^2/g, or 35 m^2/g; or wherein the taxane particles have an SSA of between about 10 m^2/g and about 60 m^2/g.

Example 6 is the method of any one of examples 1-5, wherein the taxane particles are present in a suspension, wherein the suspension comprises:

(a) the taxane particles;

(b) a pharmaceutically acceptable carrier; and

(c) a polysorbate, wherein the polysorbate is present in the suspension at a concentration of between about 0.01% v/v and about 1.5% v/v, or between about 0.01% v/v and about 1% v/v, about 0.01% v/v and about 0.5% v/v, about 0.01% v/v and about 0.4% v/v, about 0.01% v/v and about 0.25% v/v, about 0.05% v/v and about 0.5% v/v, about 0.05% v/v and about 0.25% v/v, about 0.1% v/v and about 0.5% v/v, about 0.1% v/v and about 0.25% v/v, about 0.1% v/v, about 0.16 v/v, or about 0.25% v/v.

Example 7 is the method of example 6, wherein the pharmaceutically acceptable carrier is saline, such as 0.9% sodium chloride solution.

Example 8 is the method of example 6 or 7, wherein the polysorbate is polysorbate 80.

Example 9 is the method of any one of examples 6-8, wherein the taxane is present in the suspension at a concentration between about 1 mg/ml and about 40 mg/ml, or about 6 mg/ml and about 20 mg/ml.

Example 10 is the method of any one of examples 1-9, wherein the particles and suspensions thereof are uncoated and exclude lipids, polymers, proteins such as albumin, polyethoxylated castor oil, and/or polyethylene glycol glycerides composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol.

Example 11 is the method of any one of examples 1-10, wherein the taxane comprises paclitaxel, docetaxel, cabazitaxel, or a pharmaceutically acceptable salt thereof.

Example 12 is the method of example 11, wherein the taxane comprises paclitaxel or a pharmaceutically acceptable salt thereof.

Example 13 is the method of example 12, wherein the particles have one or more of the following characteristics:

(a) a mean bulk density (not tapped) between about 0.050 g/cm^3 and about 0.12 g/cm^3, or between about 0.060 g/cm^3 and about 0.11 g/cm^3;

(b) a SSA of at least 12 m^2/g, 15 m^2/g, 18 m^2/g, 20 m^2/g, 25 m^2/g, 30 m^2/g, 32 m^2/g, 34 m^2/g, or 35 m^2/g;

(c) a SSA of between about 22 m^2/g and about 40 m^2/g, 25 m^2/g and about 40 m^2/g, 30 m^2/g and about 40 m^2/g, or between about 35 m^2/g and about 40 m^2/g; and/or

(d) wherein at least 40% (w/w) of the paclitaxel is dissolved in 30 minutes or less in a solution of 50% methanol /50% water (v/v) at 37°C and pH 7.0 in a USP II paddle apparatus operating at 75 RPM.

Example 14 is the method of example 11, wherein the taxane comprises docetaxel or a pharmaceutically acceptable salt thereof.

Example 15 is the method of example 14, wherein the particles have one or more of the following characteristics:

(a) a mean bulk density (not tapped) between about 0.050 g/cm^3 and about 0.12 g/cm^3, or between about 0.06 g/cm^3 and about 0.1 g/cm^3;

(b) a SSA of at least 12 m^2/g, 15 m^2/g, 18 m^2/g, 20 m^2/g, 25 m^2/g, 30 m^2/g, 35 m^2/g, 40 m^2/g, or 42 m^2/g;

(c) a SSA of between about 20 m^2/g and about 50 m^2/g, or between about 35 m^2/g and about 46 m^2/g; and/or

(d) wherein at least 20% (w/w) of the docetaxel is dissolved in 30 minutes or less in a solution of 15% methanol /85% water (v/v) at 37°C and pH 7.0 in a USP II paddle apparatus operating at 75 RPM.

Example 16 is the method of any one of examples 1-15, wherein the taxane remains detectable in lung tissue of the subject for at least 4 days after the administering.

Example 17 is the method of any one of examples 1-16, wherein the taxane particles are in crystalline form.

Example 18 is the method of any one of examples 1-17, wherein the taxane particles or suspensions thereof are aerosolized for administration, and the aerosol droplets have a mass median aerodynamic diameter (MMAD) of between about 0.5 µm to about 6 µm diameter, or between about 1 µm to about 3 µm diameter, or about 2 µm to about 3 µm diameter. Example 19 is the method of any one of examples 1-18, wherein the lung disorder comprises a lung tumor, and wherein the taxane particles reside at the tumor site after administration of the composition exposing the tumor to the taxane particles for a sustained amount of time sufficient to stimulate the endogenous immune system of the subject resulting in the production of tumoricidal cells and infiltration of the tumoricidal cells into the tumor at a level sufficient to treat the tumor.

Example 20 is the method of example 19, wherein the sustained amount of time is at least 4 weeks.

Example 21 is the method of any one of examples 19-20, wherein the tumoricidal cells comprise T-cells, B cells, or natural killer (NK) cells, or combinations thereof.

Example 22 is the method of any one of examples 1-21, wherein the composition is administered in two or more separate administrations.

Example 23 is the method of example 22, wherein the two or more separate administrations are administered once a week for at least two weeks.

Example 24 is the method of example 22, wherein the two or more separate administrations are administered twice a week for at least one week, wherein the two or more separate administrations are separated by at least one day.

Example 25 is the method of any one of examples 1-24, wherein the lung disorder comprises a lung tumor, and wherein the treatment of the tumor is elimination of the tumor.

Brief Description of the Figures

FIG. 1 is a graph of lung tissue and plasma levels of paclitaxel over time from inhalation study.

FIG. 2 is a plot of the aerodynamic diameter of a 6.0 mg/mL paclitaxel particle formulation from inhalation study.

FIG. 3 is a plot of the aerodynamic diameter of a 20.0 mg/mL paclitaxel particle formulation from inhalation study.

FIG. 4 is a graph of plasma levels of paclitaxel over time from inhalation study.

FIG. 5 is a graph of lung tissue levels of paclitaxel over time from inhalation study.

FIG. 6 is a graph of lung tissue and plasma levels of paclitaxel over time from inhalation study.

FIG. 7 is a diagram of a compressed air jet Hospitak nebulizer.

FIG. 8 is a graph of animal body weight over time from Orthotopic Lung Cancer study.

FIG. 9 is a graph of animal body weight change over time from Orthotopic Lung Cancer study.

FIG. 10 is a plot of animal lung weights from Orthotopic Lung Cancer study.

FIG. 11 is a plot of animal lung to body weight ratios from Orthotopic Lung Cancer study.

FIG. 12 is a plot of animal lung to brain weight ratios from Orthotopic Lung Cancer study.

FIG. 13 is a graph of average tumor areas from Orthotopic Lung Cancer study.

FIG. 14 is a plot of average tumor areas from Orthotopic Lung Cancer study.

FIG. 15 is a plot of tumor regression from Orthotopic Lung Cancer study.

FIG. 16 is a photomicrograph of Orthotopic Lung Cancer tissue slide – 1006 (Control) Adenocarcinoma-3, Primitive-1, Regression-0. Primary characteristics of the lung tumor masses. (2x).

We claim

1. Use of a composition in the manufacture of a medicament for treating a lung tumor, wherein the use comprises that an amount effective of the composition comprising taxane particles to treat the lung tumor is to be pulmonary administered to the subject, wherein the taxane particles comprise at least 95% of the taxane and have a mean particle size (number) of between 0.1 μm and 5 μm, wherein the taxane particles have a specific surface area (SSA) of at least 12 m2/g, wherein the taxane particles are present in a suspension comprising the taxane particles and a pharmaceutically acceptable carrier, wherein the suspension is aerosolized for administration, wherein the pulmonary administration comprises nebulization, and wherein the nebulization results in pulmonary delivery to the subject of aerosol droplets of the taxane particles suspension.

2. The use of claim 1, wherein the taxane particles have a mean particle size (number) of between 0.4 μm and 3 μm.

3. The use of any one of claims 1-2, wherein the taxane particles have a mean particle size (number) of between 0.4 μm and 1.2 μm.

4. The use of any one of claims 1-3, wherein the taxane particles have a specific surface area (SSA) of at least 18 m^2/g.

5. The use of any one of claims 1-4, wherein the suspension further comprises a polysorbate, wherein the polysorbate is present in the suspension at a concentration of between 0.01% v/v and 1.5% v/v.

6. The use of claim 5, wherein the pharmaceutically acceptable carrier is saline.

7. The use of claim 5 or 6, wherein the polysorbate is polysorbate 80.

8. The use of any one of claims 5-7, wherein the taxane is present in the suspension at a concentration between 1 mg/ml and 40 mg/ml.

9. The use of any one of claims 1-8, wherein the taxane particles and suspensions thereof are uncoated and exclude lipids, polymers, proteins, polyethoxylated castor oil, and polyethylene glycol glycerides composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol.

10. The use of any one of claims 1-9, wherein the taxane comprises paclitaxel, docetaxel, cabazitaxel, or a pharmaceutically acceptable salt thereof.

11. The use of claim 10, wherein the taxane comprises paclitaxel or a pharmaceutically acceptable salt thereof.

12. The use of claim 1, wherein the taxane particles have a mean bulk density between 0.050 g/cm^3 and 0.12 g/cm^3.

13. The use of claim 10, wherein the taxane comprises docetaxel or a pharmaceutically acceptable salt thereof.

14. The use of any one of claims 1-13, wherein the taxane remains detectable in lung tissue of the subject for at least 4 days after administration.

15. The use of any one of claims 1-14, wherein the taxane particles are in crystalline form.

16. The use of any one of claims 1-15, wherein the aerosol droplets have a mass median aerodynamic diameter (MMAD) of between 0.5 μm to 6 μm diameter.

17. The use of any one of claims 1-16, wherein the taxane particles reside at the tumor site after administration of the composition exposing the tumor to the taxane particles for a sustained amount of time sufficient to stimulate the endogenous immune system of the subject resulting in the production of tumoricidal cells and infiltration of the tumoricidal cells into the tumor at a level sufficient to treat the tumor.

18. The use of claim 17, wherein the sustained amount of time is at least 4 weeks.

19. The use of any one of claims 17-18, wherein the tumoricidal cells comprise T-cells, B cells, or natural killer (NK) cells, or combinations thereof.

20. The use of any one of claims 1-19, wherein the composition is to be administered in two or more separate administrations.

21. The use of claim 20, wherein the composition is to be administered once a week for at least two weeks.

22. The use of claim 20, wherein the composition is to be administered twice a week for at least one week, wherein the two or more separate administrations are separated by at least one day.

23. The use of any one of claims 1-22, wherein the treatment of the tumor is elimination of the tumor.