~~COMBINATIONS AND MODES OF ADMINISTRATION OF THERAPEUTIC AGENTS AND COMBINATION THERAPY~~NANOPARTICLE COMPOSITION COMPRISING AN ANTI-CANCER AGENT AND A CARRIER PROTEIN

RELATED APPLICATIONS

[0001] This application claims priority benefit to provisional application 60/654,245, filed on February 18, 2005.

TECHNICAL FIELD

[0002] The present invention relates to methods and compositions for the treatment of proliferative diseases comprising the administration of a combination of a taxane and at least one other and other therapeutic agents, as well as other treatment modalities useful in the treatment of proliferative diseases. In particular, the invention relates to the use of nanoparticles comprising paclitaxel and albumin (such as Abraxane™) in combination with other chemotherapeutic agents or radiation, which may be used for the treatment of cancer.

BACKGROUND

[0003] The failure of a significant number of tumors to respond to drug and/or radiation therapy is a serious problem in the treatment of cancer. In fact, this is one of the main reasons why many of the most prevalent forms of human cancer still resist effective chemotherapeutic intervention, despite certain advances in the field of chemotherapy.

[0004] Cancer is now primarily treated with one or a combination of three types of therapies: surgery, radiation, and chemotherapy. Surgery is a traditional approach in which all or part of a tumor is removed from the body. Surgery generally is only effective for treating the earlier stages of cancer. While surgery is sometimes effective in removing tumors located at certain sites, for example, in the breast, colon, and skin, it cannot be used in the treatment of tumors located in other areas, inaccessible to surgeons, nor in the treatment of disseminated neoplastic conditions such as leukemia. For more than 50% of cancer individuals, by the time they are diagnosed they are no longer candidates for effective surgical treatment. Surgical procedures may increase tumor metastases through blood circulation during surgery. Most of cancer individuals do not die from the cancer at the time of diagnosis or surgery, but rather die from the metastasis and the recurrence of the cancer.

[0005] Other therapies are also often ineffective. Radiation therapy is only effective for individuals who present with clinically localized disease at early and middle

[0027] More effective treatments for proliferative diseases, especially cancer, are needed.

BRIEF SUMMARY OF THE INVENTION

[0028] In a first aspect, the present invention refers to the use of a composition comprising nanoparticles comprising a) rapamycin or 17-AAG, and b) a carrier protein, for the manufacture of a medicament for treating a proliferative disease, wherein the composition is used in combination with nanoparticles comprising a taxane and a carrier protein.

[0029] Described herein are~~The present invention provides~~ methods for the treatment of proliferative diseases such as cancer. Described herein are~~The invention provides~~ combination therapy methods of treating proliferative diseases (such as cancer), comprising a) a first therapy comprising administering to an individual an effective amount of a composition comprising nanoparticles comprising a taxane (such as paclitaxel) and a carrier protein (such as albumin) and b) a second therapy, such as chemotherapy, radiation therapy, surgery, or combinations thereof. In another example~~aspect~~, there are provided methods of administering to an individual a composition comprising nanoparticles comprising a taxane (such as paclitaxel) and a carrier protein (such as albumin) based on a metronomic dosing regime.

[0030] In some example~~embodiments~~, it is described~~the invention provides~~ a method of treating a proliferative disease (such as cancer) in an individual comprising administering to the individual a) an effective amount of a composition comprising nanoparticles comprising a taxane and a carrier protein (such as albumin), and b) an effective amount of at least one other chemotherapeutic agent. In some example~~embodiments~~, it is described~~the invention provides~~ a method of treating a proliferative disease (such as cancer) in an individual comprising administering to the individual a) an effective amount of a composition comprising nanoparticles comprising paclitaxel and an albumin (such as Abraxane™), and b) an effective amount of at least one other chemotherapeutic agent, hi some embodiments, the chemotherapeutic agent is any of (and in some embodiments selected from the group consisting of} antimetabolites (including nucleoside analogs), platinum-based agents, alkylating agents, tyrosine kinase inhibitors, anthracycline antibiotics, vinca alkloids, proteasome inhibitors, macrolides, and topoisomerase inhibitors. In some example~~embodiments~~, the chemotherapeutic agent is a platinum-based agent, such as carboplatin.

[0031] In some example~~embodiments~~, the composition comprising nanoparticles (also referred to as "nanoparticle composition") and the chemotherapeutic agent are administered simultaneously, either in the same composition or in separate compositions. In some example~~embodiments~~, the nanoparticle composition and the chemotherapeutic agent are

administered sequentially, i.e., the nanoparticle composition is administered either prior to or after the administration of the chemotherapeutic agent. In some example~~embodiments~~, the administration of the nanoparticle composition and the chemotherapeutic agent are concurrent, i.e., the administration period of the nanoparticle composition and that of the chemotherapeutic agent overlap with each other. In some example~~embodiments~~, the administration of the nanoparticle composition and the chemotherapeutic agent are non-concurrent. For example, in some example~~embodiments~~, the administration of the nanoparticle composition is terminated before the chemotherapeutic agent is administered. In some example~~embodiments~~, the administration of the chemotherapeutic agent is terminated before the nanoparticle composition is administered.

[0032] In some example~~embodiments~~, the first therapy taxane is nano-particle albumin bound paxlitaxel, described, for example, in U.S. Patent 6,566,405, and commercially available under the tradename Abraxane™. In addition, the first therapy taxane is also considered to be nanoparticle albumin bound docetaxel described for example in U.S. Patent Application Publication 2005/0004002A1.

[0033] In another example, it is described~~aspect, there is provided~~ a method of treating a proliferative disease (such as cancer) in an individual comprising a) a first therapy comprising administering to the individual a composition comprising nanoparticles comprising a taxane and a carrier protein (such as albumin), and b) a second therapy comprising radiation therapy, surgery, or combinations thereof. In some example~~embodiments~~, there is provided a method of treating a proliferative disease (such as cancer) in an individual comprising a) a first therapy comprising administering to the individual a composition comprising nanoparticles comprising paclitaxel and an albumin (such as Abraxane™), and b) a second therapy comprising radiation therapy, surgery, or combinations thereof. In some example~~embodiments~~, the second therapy is radiation therapy. In some example~~embodiments~~, the second therapy is surgery. In some example~~embodiments~~, the first therapy is carried out prior to the second therapy. In some examples~~mbodiments~~, the first therapy is carried out after the second therapy.

[0034] In another example~~aspect~~, the method comprises administering to a mammal having a proliferative disease (such as cancer) a combination therapy comprising a first therapy comprising a taxane and a second therapy selected from the group consisting of chemotherapeutic agent and radiation or combinations thereof. The combination therapy may be administered in any of a variety of ways such as sequentially or simultaneously, and if sequential, the taxane may be administered before or after the second therapy

although it is preferred that the first therapy comprising a taxane is administered first. It will also be understood that the second therapy can include more than one chemotherapeutic agent.

[0035] The present disclosure~~invention~~ also describes~~provides~~ metronomic therapy regimes. In some examples, it is described~~embodiments, there is provided~~ a method of administering a composition comprising nanoparticles comprising a taxane and a carrier protein (such as albumin), wherein the nanoparticle composition is administered over a period of at least one month, wherein the interval between each administration is no more than about a week, and wherein the dose of taxane at each administration is about 0.25% to about 25% of its maximum tolerated dose following a traditional dosing regime. In some example~~embodiments~~, it is described~~there is provided~~ a method of administering a composition comprising nanoparticles comprising paclitaxel and an albumin (such as Abraxane™), wherein the nanoparticle composition is administered over a period of at least one month, wherein the interval between each administration is no more than about a week, and wherein the dose of paclitaxel at each administration is about 0.25% to about 25% of its maximum tolerated dose following a traditional dosing regime. In some example~~embodiments~~, the dose of the taxane (such as paclitaxel, for example Abraxane™) per administration is less than about any of 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 18%, 20%, 22%, 24%, or 25% of the maximum tolerated dose. In some example~~embodiments~~, the nanoparticle composition is administered at least about any of 1x, 2x, 3x, 4x, 5x, 6x, 7x (i.e., daily) a week. In some example~~embodiments~~, the intervals between each administration are less than about any of 7 days, 6 days, 5 days, 4 days, 3 days, 2 days, and 1 day. In some example~~embodiments~~, the nanoparticle composition is administered over a period of at least about any of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 18, 24, 30 and 36 months.

[0036] In some example~~embodiments~~, there is provided a method of administering a composition comprising nanoparticles comprising a taxane and a carrier protein (such as albumin), wherein the taxane is administered over a period of at least one month, wherein the interval between each administration is no more than about a week, and wherein the dose of the taxane at each administration is about 0.25 mg/m^2 to about 25 mg/m^2. In some example~~embodiments~~, there is provided a method of administering a composition comprising nanoparticles comprising paclitaxel and an albumin (such as Abraxane™) and a carrier protein (such as albumin), wherein the paclitaxel is administered over a period of at least one month, wherein the interval between each administration is no more than about a week, and wherein the dose of the taxane at each administration is about 0.25 mg/m^2 to about 25

mg/m^2. In some examplembodiments, the dose of the taxane (such as paclitaxel, for example Abraxane^{TM}) per administration is less than about any of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 18, 20, 22, and 25 mg/m^2. In some examplembodiments, the nanoparticle composition is administered at least about any of 1x, 2x, 3x, 4x, 5x, 6x, 7x (i.e., daily) a week. In some examplembodiments, the intervals between each administration are less than about any of 7 days, 6 days, 5 days, 4 days, 3 days, 2 days, and 1 day. In some examplembodiments, the nanoparticle composition is administered over a period of at least about any of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 18, 24, 30 and 36 months.

[0037] The methods ~~of the invention~~ generally comprise administration of a composition comprising nanoparticles comprising a taxane and a carrier protein. In some examplembodiments, the nanoparticle composition comprises nanoparticles comprising paclitaxel and an albumin. In some examplesmbodiments, the paclitaxel/albumin nanoparticles have an average diameter of no greater than about 200 nm. In some examplembodiments, the paclitaxel/albumin nanoparticle composition is substantially free (such as free) of surfactant (such as Cremophor). In some examplembodiments, the weight ratio of the albumin to paclitaxel in the composition is about 18:1 or less, such as about 9:1 or less. In some examplembodiments, the paclitaxel is coated with albumin. In some exampleembodiments, the paclitaxel/albumin nanoparticles have an average diameter of no greater than about 200 nm and the paclitaxel/albumin composition is substantially free (such as free) of surfactant (such as Cremophor). In some examplembodiments, the paclitaxel/albumin nanoparticles have an average diameter of no greater than about 200 nm and the paclitaxel is coated with albumin, Other combinations of the above characteristics are also contemplated. In some examplembodiments, the nanoparticle composition is Abraxane^{TM}. Nanoparticle compositions comprising other taxanes (such as docetaxel and ortataxel) may also comprise one or more of the above characteristics.

[0038] These and other aspects and advantages of the present invention will become apparent from the subsequent detailed description and the appended claims. It is to be understood that one, some, or all of the properties of the various embodiments described herein may be combined to form other embodiments of the present invention.

BRIEF DESCRIPTION OF FIGURES

[0039] Figure 1A shows the effect of ABI-007 on rat aortic ring angiogenesis. Figure 1B shows the effect of ABI-007 on human endothelial cell proliferation. Figure 1C shows the effect of ABI-007 on endothelial cell tube formation.

WHAT WE CLAIM IS:

1. Use of a composition comprising nanoparticles comprising a) thiocolchicine or derivative thereof, rapamycin, or 17-AAG, and b) a carrier protein, for the manufacture of a medicament for treating a proliferative disease, wherein the composition is used in combination with nanoparticles comprising a taxane and a carrier protein.

2. The use of claim 1, wherein the average diameter of the nanoparticles in a) is no greater than about 200 nm.

3. The use of claim 1 or claim 2, wherein the nanoparticles in a) are sterile filterable.

4. The use of any one of claims 1 to 3, wherein the nanoparticles in a) are coated with the carrier protein.

5. The use of any one of claims 1 to 4, wherein the carrier protein is albumin.

6. The use of claim 5, wherein the albumin is human serum albumin.

7. The use of any one of claims 1 to 6, wherein the proliferative disease is cancer.

8. The use of claim 7, wherein the cancer is lung cancer.

9. The use of claim 7, wherein the cancer is breast cancer.

10. The use of claim 7, wherein the cancer is colon cancer.

11. The use of claim 7, wherein the cancer is ovarian cancer.

12. The use of claim 7, wherein the cancer is pancreatic cancer.

13. The use of claim 7, wherein the cancer is melanoma.

14. The use of any of claims 7 to 13, wherein the proliferative disease is a cancer that is resistant to treatment by paclitaxel or docetaxel.

15. The use of any one of claims 1 to 14, wherein the nanoparticles in a) comprise thiocolchicine or derivative thereof.

16. The use of claim 15, wherein the nanoparticles in a) comprise thiocolchicine.

17. The use of any one of claims 1 to 14, wherein the nanoparticles in a) comprise rapamycin.

18. The use of any one of claims 1 to 14, wherein the nanoparticles in a) comprise 17-AAG.

WHAT WE CLAIM IS:

1. Use of a composition comprising nanoparticles comprising a) rapamycin or 17-AAG, and b) a carrier protein, for the manufacture of a medicament for treating a proliferative disease, wherein the composition is used in combination with nanoparticles comprising a taxane and a carrier protein.

2. The use of claim 1, wherein the average diameter of the nanoparticles in a) is no greater than about 200 nm.

3. The use of claim 1 or claim 2, wherein the nanoparticles in a) are sterile filterable.

4. The use of any one of claims 1 to 3, wherein the nanoparticles in a) are coated with the carrier protein.

5. The use of any one of claims 1 to 4, wherein the carrier protein is albumin.

6. The use of claim 5, wherein the albumin is human serum albumin.

7. The use of any one of claims 1 to 6, wherein the proliferative disease is cancer.

8. The use of claim 7, wherein the cancer is lung cancer.

9. The use of claim 7, wherein the cancer is breast cancer.

10. The use of claim 7, wherein the cancer is colon cancer.

11. The use of claim 7, wherein the cancer is ovarian cancer.

12. The use of claim 7, wherein the cancer is pancreatic cancer.

13. The use of claim 7, wherein the cancer is melanoma.

14. The use of any one of claims 1 to 13, wherein the nanoparticles in a) comprise rapamycin.

15. The use of any one of claims 1 to 13, wherein the nanoparticles in a) comprise 17-AAG.