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(54) METHODS AND COMPOSITIONS USING IMMUNOMODULATORY COMPOUNDS FOR TREATMENT AND MANAGEMENT OF CANCERS AND OTHER DISEASES

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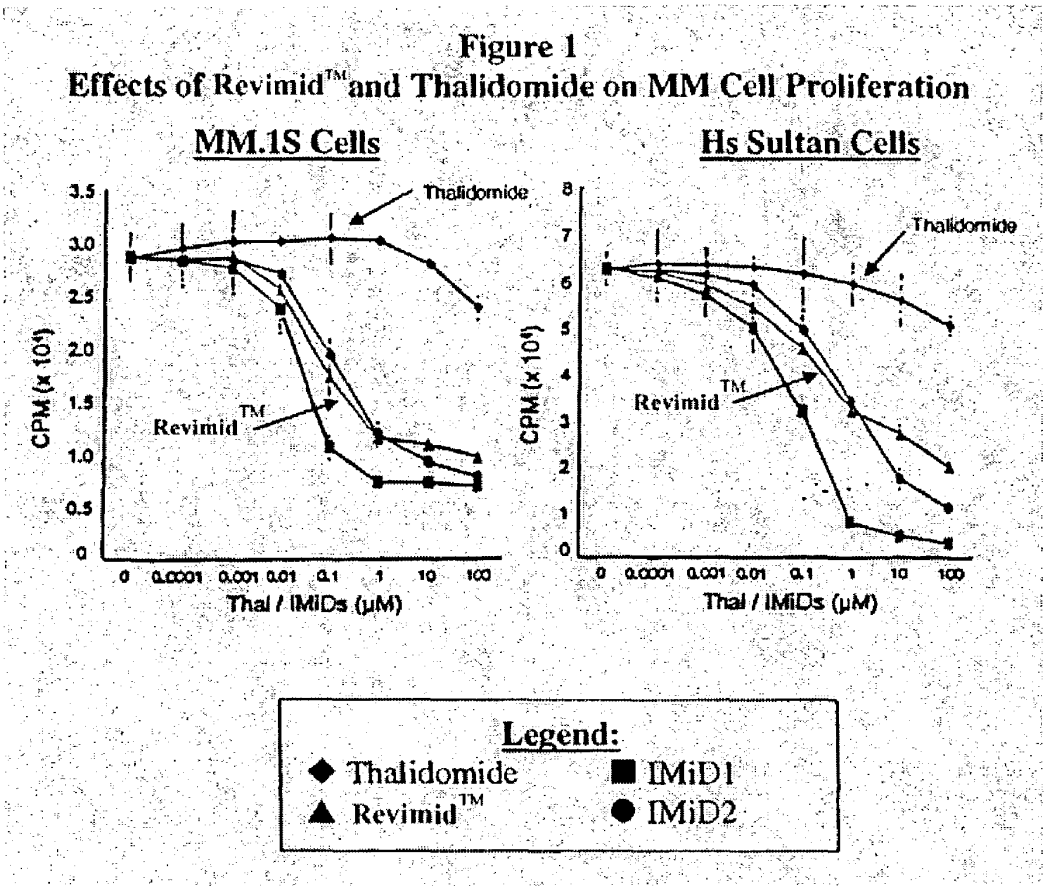
(57) **ABSTRACT**

Methods of treating, preventing and/or managing cancer as well as and diseases and disorders associated with, or characterized by, undesired angiogenesis are disclosed. Specific methods encompass the administration of an immunomodulatory compound alone or in combination with a second active ingredient. The invention further relates to methods of reducing or avoiding adverse side effects associated with chemotherapy, radiation therapy, hormonal therapy, biological therapy or immunotherapy which comprise the administration of an immunomodulatory compound. Pharmaceutical compositions, single unit dosage forms, and kits suitable for use in methods of the invention are also disclosed.

Figure 1

Effects of Revimid™ and Thalidomide on MM Cell Proliferation



METHODS AND COMPOSITIONS USING IMMUNOMODULATORY COMPOUNDS FOR TREATMENT AND MANAGEMENT OF CANCERS AND OTHER DISEASES

[0001] This application claims the benefit of U.S. provisional application No. 60/380,842, filed May 17, 2002, and No. 60/424,600, filed Nov. 6, 2002, the entireties of which are incorporated herein by reference.

1. Field of the Invention

[0002] This invention relates to methods of treating, preventing and/or managing specific cancers, and other diseases including, but not limited to, those associated with, or characterized by, undesired angiogenesis, by the administration of one or more immunomodulatory compounds alone or in combination with other therapeutics. In particular, the invention encompasses the use of specific combinations, or "cocktails," of drugs and other therapy, e.g., radiation to treat these specific cancers, including those refractory to conventional therapy. The invention also relates to pharmaceutical compositions and dosing regimens.

2. BACKGROUND OF THE INVENTION

[0003] 2.1 Pathobiology of Cancer and Other Diseases

[0004] Cancer is characterized primarily by an increase in the number of abnormal cells derived from a given normal tissue, invasion of adjacent tissues by these abnormal cells, or lymphatic or blood-borne spread of malignant cells to regional lymph nodes and to distant sites (metastasis). Clinical data and molecular biologic studies indicate that cancer is a multistep process that begins with minor preneoplastic changes, which may under certain conditions progress to neoplasia. The neoplastic lesion may evolve clonally and develop an increasing capacity for invasion, growth, metastasis, and heterogeneity, especially under conditions in which the neoplastic cells escape the host's immune surveillance. Roitt, I., Brostoff, J and Kale, D., *Immunology,* 17.1-17.12 (3rd ed., Mosby, St. Louis, Mo., 1993).

[0005] There is an enormous variety of cancers which are described in detail in the medical literature. Examples includes cancer of the lung, colon, rectum, prostate, breast, brain, and intestine. The incidence of cancer continues to climb as the general population ages, as new cancers develop, and as susceptible populations (e.g., people infected with AIDS or excessively exposed to sunlight) grow. A tremendous demand therefore exists for new methods and compositions that can be used to treat patients with cancer.

[0006] Many types of cancers are associated with new blood vessel formation, a process known as angiogenesis. Several of the mechanisms involved in tumor-induced angiogenesis have been elucidated. The most direct of these mechanisms is the secretion by the tumor cells of cytokines with angiogenic properties. Examples of these cytokines include acidic and basic fibroblastic growth factor (a,b-FGF), angiogenin, vascular endothelial growth factor (VEGF), and TNF-α. Alternatively, tumor cells can release angiogenic peptides through the production of proteases and the subsequent breakdown of the extracellular matrix where some cytokines are stored (e.g., b-FGF). Angiogenesis can also be induced indirectly through the recruitment of inflammatory cells (particularly macrophages) and their subsequent release of angiogenic cytokines (e.g., TNF-α, bFGF).

[0007] A variety of other diseases and disorders are also associated with, or characterized by, undesired angiogenesis. For example, enhanced or unregulated angiogenesis has been implicated in a number of diseases and medical conditions including, but not limited to, ocular neovascular diseases, choroidal neovascular diseases, retina neovascular diseases, rubeosis (neovascularization of the angle), viral diseases, genetic diseases, inflammatory diseases, allergic diseases, and autoimmune diseases. Examples of such diseases and conditions include, but are not limited to: diabetic retinopathy; retinopathy of prematurity; corneal graft rejection; neovascular glaucoma; retrolental fibroplasia; and proliferative vitreoretinopathy.

[0008] Accordingly, compounds that can control angiogenesis or inhibit the production of certain cytokines, including TNF-α, may be useful in the treatment and prevention of various diseases and conditions.

[0009] 2.2 Methods of Treating Cancer

[0010] Current cancer therapy may involve surgery, chemotherapy, hormonal therapy and/or radiation treatment to eradicate neoplastic cells in a patient (see, for example, Stockdale, 1998, *Medicine, vol.* 3, Rubenstein and Federman, eds., Chapter 12, Section IV). Recently, cancer therapy could also involve biological therapy or immunotherapy. All of these approaches pose significant drawbacks for the patient. Surgery, for example, may be contraindicated due to the health of a patient or may be unacceptable to the patient. Additionally, surgery may not completely remove neoplastic tissue. Radiation therapy is only effective when the neoplastic tissue exhibits a higher sensitivity to radiation than normal tissue. Radiation therapy can also often elicit serious side effects. Hormonal therapy is rarely given as a single agent. Although hormonal therapy can be effective, it is often used to prevent or delay recurrence of cancer after other treatments have removed the majority of cancer cells. Biological therapies and immunotherapies are limited in number and may produce side effects such as rashes or swellings, flu-like symptoms, including fever, chills and fatigue, digestive tract problems or allergic reactions.

[0011] With respect to chemotherapy, there are a variety of chemotherapeutic agents available for treatment of cancer. A majority of cancer chemotherapeutics act by inhibiting DNA synthesis, either directly, or indirectly by inhibiting the biosynthesis of deoxyribonucleotide triphosphate precursors, to prevent DNA replication and concomitant cell division. Gilman et al., *Goodman and Gilman 's: The Pharmacological Basis of Therapeutics,* Tenth Ed. (McGraw Hill, New York).

[0012] Despite availability of a variety of chemotherapeutic agents, chemotherapy has many drawbacks. Stockdale, *Medicine,* vol. 3, Rubenstein and Federman, eds., ch. 12, sect. 10, 1998. Almost all chemotherapeutic agents are toxic, and chemotherapy causes significant, and often dangerous side effects including severe nausea, bone marrow depression, and immunosuppression. Additionally, even with administration of combinations of chemotherapeutic agents, many tumor cells are resistant or develop resistance to the chemotherapeutic agents. In fact, those cells resistant to the

particular chemotherapeutic agents used in the treatment protocol often prove to be resistant to other drugs, even if those agents act by different mechanism from those of the drugs used in the specific treatment. This phenomenon is referred to as pleiotropic drug or multidrug resistance. Because of the drug resistance, many cancers prove refractory to standard chemotherapeutic treatment protocols.

[0013] Other diseases or conditions associated with, or characterized by, undesired angiogenesis are also difficult to treat. However, some compounds such as protamine, hepain and steroids have been proposed to be useful in the treatment of certain specific diseases. Taylor et al., *Nature* 297:307 (1982); Folkman et al., *Science* 221:719 (1983); and U.S. Pat. Nos. 5,001,116 and 4,994,443. Thalidomide and certain derivatives of it have also been proposed for the treatment of such diseases and conditions. U.S. Pat. Nos. 5,593,990, 5,629,327, 5,712,291, 6,071,948 and 6,114,355 to D'Amato.

[0014] Still, there is a significant need for safe and effective methods of treating, preventing and managing cancer and other diseases and conditions, particularly for diseases that are refractory to standard treatments, such as surgery, radiation therapy, chemotherapy and hormonal therapy, while reducing or avoiding the toxicities and/or side effects associated with the conventional therapies.

[0015] 2.3 IMIDS™

[0016] A number of studies have been conducted with the aim of providing compounds that can safely and effectively be used to treat diseases associated with abnormal production of TNF-α See, e.g., Marriott, J. B., et al., *Expert Opin. Biol. Ther.* 1(4):1-8 (2001); G. W. Muller, et al., Journal of Medicinal Chemistry 39(17): 3238-3240 (1996); and G. W. Muller, et al, Bioorganic & Medicinal Chemistry Letters 8: 2669-2674 (1998). Some studies have focused on a group of compounds selected for their capacity to potently inhibit TNF-α production by LPS stimulated PBMC. L. G. Corral, et al., Ann. Rheum. Dis. 58:(Suppl I) 1107-1113 (1999). These compounds, which are referred to as IMiDS™ (Celgene Corporation) or Immunomodulatory Drugs, show not only potent inhibition of TNF-α but also marked inhibition of LPS induced monocyte IL1β and IL12 production. LPS induced IL6 is also inhibited by immunomodulatory compounds, albeit partially. These compounds are potent stimulators of LPS induced IL10. Id. Particular examples of IMiD™s include, but are not limited to, the substituted 2-(2,6-dioxopiperidin-3-yl) phthalimides and substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindoles described in U.S. Pat. Nos. 6,281,230 and 6,316,471, both to G. W. Muller, et al.

3. SUMMARY OF THE INVENTION

[0017] This invention encompasses methods of treating and preventing certain types of cancer, including primary and metastatic cancer, as well as cancers that are refractory or resistant to conventional chemotherapy. The methods comprise administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof. The invention also encompasses methods of managing certain cancers (e.g., preventing or prolonging their recurrence, or lengthening the time of remission) which comprise administering to a patient in need of such management a prophylactically effective amount of an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

[0018] In particular methods of the invention, an immunomodulatory compound is administered in combination with a therapy conventionally used to treat, prevent or manage cancer. Examples of such conventional therapies include, but are not limited to, surgery, chemotherapy, radiation therapy, hormonal therapy, biological therapy and immunotherapy.

[0019] This invention also encompasses methods of treating, managing or preventing diseases and disorders other than cancer that are associated with, or characterized by, undesired angiogenesis, which comprise administering to a patient in need of such treatment, management or prevention a therapeutically or prophylactically effective amount of an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

[0020] In other methods of the invention, an immunomodulatory compound is administered in combination with a therapy conventionally used to treat, prevent or manage diseases or disorders associated with, or characterized by, undesired angiogenesis. Examples of such conventional therapies include, but are not limited to, surgery, chemotherapy, radiation therapy, hormonal therapy, biological therapy and immunotherapy.

[0021] This invention encompasses pharmaceutical compositions, single unit dosage forms, dosing regimens and kits which comprise an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, and a second, or additional, active agent. Second active agents include specific combinations, or "cocktails," of drugs.

4. BRIEF DESCRIPTION OF FIGURE

[0022] **FIG. 1** shows a comparison of the effects of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2, 6-dione (Revimid™) and thalidomide in inhibiting the proliferation of multiple myeloma (MM) cell lines in an in vitro study. The uptake of [^{3}H]-thymidine by different MM cell lines (MM. 1S, Hs Sultan, U266 and RPMI-8226) was measured as an indicator of the cell proliferation.

5. DETAILED DESCRIPTION OF THE INVENTION

[0023] A first embodiment of the invention encompasses methods of treating, managing, or preventing cancer which comprises administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

[0024] In particular methods encompassed by this embodiment, the immunomodulatory compound is administered in combination with another drug ("second active agent") or method of treating, managing, or preventing cancer. Second active agents include small molecules and large molecules (e.g., proteins and antibodies), examples of which are provided herein, as well as stem cells. Methods,

or therapies, that can be used in combination with the administration of the immunomodulatory compound include, but are not limited to, surgery, blood transfusions, immunotherapy, biological therapy, radiation therapy, and other non-drug based therapies presently used to treat, prevent or manage cancer.

[0025] Another embodiment of the invention encompasses methods of treating, managing or preventing diseases and disorders other than cancer that are characterized by undesired angiogenesis. These methods comprise the administration of a therapeutically or prophylactically effective amount of an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

[0026] Examples of diseases and disorders associated with, or characterized by, undesired angiogenesis include, but are not limited to, inflammatory diseases, autoimmune diseases, viral diseases, genetic diseases, allergic diseases, bacterial diseases, ocular neovascular diseases, choroidal neovascular diseases, retina neovascular diseases, and rubeosis (neovascularization of the angle).

[0027] In particular methods encompassed by this embodiment, the immunomodulatory compound is administer in combination with a second active agent or method of treating, managing, or preventing the disease or condition. Second active agents include small molecules and large molecules (e.g., proteins and antibodies), examples of which are provided herein, as well as stem cells. Methods, or therapies, that can be used in combination with the administration of the immunomodulatory compound include, but are not limited to, surgery, blood transfusions, immunotherapy, biological therapy, radiation therapy, and other non-drug based therapies presently used to treat, prevent or manage disease and conditions associated with, or characterized by, undesired angiogenesis.

[0028] The invention also encompasses pharmaceutical compositions (e.g., single unit dosage forms) that can be used in methods disclosed herein. Particular pharmaceutical compositions comprise an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, and a second active agent.

[0029] 5.1 Immunomodulatory Compounds

[0030] Compounds used in the invention include immunomodulatory compounds that are racemic, stereomerically enriched or stereomerically pure, and pharmaceutically acceptable salts, solvates, hydrates, stereoisomers, clathrates, and prodrugs thereof. Preferred compounds used in the invention are small organic molecules having a molecular weight less than about 1,000 g/mol, and are not proteins, peptides, oligonucleotides, oligosaccharides or other macromolecules.

[0031] As used herein and unless otherwise indicated, the terms "immunomodulatory compounds" and "IMiDs™" (Celgene Corporation) encompasses small organic molecules that markedly inhibit TNF-α, LPS induced monocyte IL1β and IL12, and partially inhibit IL6 production. Specific immunomodulatory compounds are discussed below.

[0032] TNF-α is an inflammatory cytokine produced by macrophages and monocytes during acute inflammation. TNF-α is responsible for a diverse range of signaling events within cells. TNF-α may play a pathological role in cancer. Without being limited by theory, one of the biological effects exerted by the immunomodulatory compounds of the invention is the reduction of synthesis of TNF-α. Immunomodulatory compounds of the invention enhance the degradation of TNF-αmRNA.

[0033] Further, without being limited by theory, immunomodulatory compounds used in the invention may also be potent co-stimulators of T cells and increase cell proliferation dramatically in a dose dependent manner. Immunomodulatory compounds of the invention may also have a greater co-stimulatory effect on the CD8+ T cell subset than on the CD4+ T cell subset. In addition, the compounds preferably have anti-inflammatory properties, and efficiently co-stimulate T cells.

[0034] Specific examples of immunomodulatory compounds of the invention, include, but are not limited to, cyano and carboxy derivatives of substituted styrenes such as those disclosed in U.S. Pat. No. 5,929,117; 1-oxo-2-(2,6-dioxo-3-fluoropiperidin-3yl) isoindolines and 1,3-dioxo-2-(2,6-dioxo-3-fluoropiperidine-3-yl) isoindolines such as those described in U.S. Pat. No. 5,874,448; the tetra substituted 2-(2,6-dioxopiperdin-3-yl)-1-oxoisoindolines described in U.S. Pat. No. 5,798,368; 1-oxo and 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl) isoindolines (e.g., 4-methyl derivatives of thalidomide and EM-12), including, but not limited to, those disclosed in U.S. Pat. No. 5,635,517; and a class of non-polypeptide cyclic amides disclosed in U.S. Pat. Nos. 5,698,579 and 5,877,200; analogs and derivatives of thalidomide, including hydrolysis products, metabolites, derivatives and precursors of thalidomide, such as those described in U.S. Pat. Nos. 5,593,990, 5,629,327, and 6,071,948 to D'Amato; aminothalidomide, as well as analogs, hydrolysis products, metabolites, derivatives and precursors of aminothalidomide, and substituted 2-(2,6-dioxopiperidin-3-yl) phthalimides and substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindoles such as those described in U.S. Pat. Nos. 6,281,230 and 6,316,471; isoindole-imide compounds such as those described in U.S. patent application Ser. No. 09/972,487 filed on Oct. 5, 2001, U.S. patent application Ser. No. 10/032,286 filed on Dec. 21, 2001, and International Application No. PCT/US01/50401 (International Publication No. WO 02/059106). The entireties of each of the patents and patent applications identified herein are incorporated herein by reference. Immunomodulatory compounds of the invention do not include thalidomide.

[0035] Other specific immunomodulatory compounds of the invention include, but are not limited to, 1-oxo-and 1,3 dioxo-2-(2,6-dioxopiperidin-3-yl) isoindolines substituted with amino in the benzo ring as described in U.S. Pat. No. 5,635,517 which is incorporated herein by reference. These compounds have the structure I:

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