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(54) **COMPOSITIONS AND METHODS FOR THE TREATMENT OF CANCER**

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(57) **ABSTRACT**

This invention relates to compositions comprising thalidomide and another anti-cancer drug which can be used in the treatment or prevention of cancer. Preferred anti-cancer drugs are topoisomerase inhibitors. A particular composition comprises thalidomide, or a pharmaceutically acceptable salt, solvate, or clathrate thereof, and irinotecan. The invention also relates to methods of treating or preventing cancer which comprise the administration of a thalidomide and another anti-cancer drug to a patient in need of such treatment or prevention. The invention further relates to methods of reducing or avoiding adverse side effects associated with the administration of chemotherapy or radiation therapy which comprise the administration of thalidomide to a patient in need of such reduction or avoidance.

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## COMPOSITIONS AND METHODS FOR THE TREATMENT OF CANCER

### 1. FIELD OF THE INVENTION

[0001] This invention relates to pharmaceutical compositions comprising thalidomide and an anti-cancer agent, particularly a topoisomerase inhibitor, to methods of treating cancer, and to methods of reducing or avoiding adverse effects associated with anti-cancer agents such as topoisomerase inhibitors.

### 2. BACKGROUND OF THE INVENTION

[0002] 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) grow. A tremendous demand therefore exists for new methods and compositions that can be used to treat patients with cancer.

#### 2.1. PATHOBIOLOGY OF CANCER

[0003] 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 pre-neoplastic changes, which may under certain conditions progress to neoplasia.

[0004] Pre-malignant abnormal cell growth is exemplified by hyperplasia, metaplasia, or most particularly, dysplasia (for review of such abnormal growth conditions, see Robbins and Angell, 1976, *Basic Pathology*, 2d Ed., W. B. Saunders Co., Philadelphia, pp. 68-79). Hyperplasia is a form of controlled cell proliferation involving an increase in cell number in a tissue or organ, without significant alteration in structure or function. As but one example, endometrial hyperplasia often precedes endometrial cancer. Metaplasia is a form of controlled cell growth in which one type of adult or fully differentiated cell substitutes for another type of adult cell. Metaplasia can occur in epithelial or connective tissue cells. Atypical metaplasia involves a somewhat disorderly metaplastic epithelium. Dysplasia is frequently a forerunner of cancer, and is found mainly in the epithelia; it is the most disorderly form of non-neoplastic cell growth, involving a loss in individual cell uniformity and in the architectural orientation of cells. Dysplastic cells often have abnormally large, deeply stained nuclei, and exhibit pleomorphism. Dysplasia characteristically occurs where there exists chronic irritation or inflammation, and is often found in the cervix, respiratory passages, oral cavity, and gall bladder.

[0005] 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: 1993).

[0006] Descriptions of only a few types of cancers are provided below. Characteristics of other types of cancers are well known to medical practitioners, and are described in the medical literature.

### 2.2. AIDS-RELATED NON-HODGKIN'S LYMPHOMA

[0007] AIDS has been closely associated with a variety of cancers. Further, the types of malignancies and their incidence rates are increasing as the development of effective antiretroviral therapies and prophylaxis against opportunistic infections leads to prolonged survival in the immunodeficient state for AIDS patients. Karp and Broder, *Cancer Res.* 51:4747-4756 (1991). AIDS-related non-Hodgkin's lymphoma is a very aggressive disease with a very high incidence of central nervous system involvement. Since its discovery in 1981, the incidence of AIDS-related non-Hodgkin's lymphoma has reportedly increased. One reason for such an observation is that patients infected with the AIDS virus now live longer than they used to.

### 2.3. PRIMARY AND METASTATIC CNS TUMORS

[0008] The incidence of primary and metastatic brain tumors is also increasing in the United States. Unfortunately, the arsenal of chemotherapeutics for these types of cancers is minimal, while the need for such therapeutics is high.

[0009] Glioblastoma multiform and other primary and metastatic central nervous system tumors are devastating malignancies. The treatment of these tumors include surgery, radiation therapy and treatment with agents such as the nitrosourea BCNU. Other chemotherapeutic agents utilized include procarbazine, vincristine, hydroxyurea and cisplatin. But even when all three modalities (surgery, radiation therapy and chemotherapy) are utilized, the average survival of patients with central nervous system malignancies is only about 57 weeks. Clearly, new treatment approaches are needed both for patients with newly diagnosed primary and metastatic central nervous system tumors, as well as for patients with such tumors which are refractory to the above modalities.

### 2.4. BREAST, LUNG, BLADDER AND PROSTATE CANCERS

[0010] In the United States, the cumulative risk of developing breast cancer is reportedly about 10.2 percent. *The Merck Manual* 1815 (16<sup>th</sup> ed. 1992). The treatment for early breast cancer is surgery, with or without radiation therapy, or surgery, with or without radiation therapy, plus chemotherapy and/or hormonal therapy. Current chemotherapy for patients with primary or metastatic breast cancer includes treatment with cyclophosphamide, methotrexate, doxorubicin, 5-fluorouracil, cisplatin, vinblastine, taxol, taxotere, mitomycin C and occasionally other agents. Unfortunately, even with these agents, almost all women who develop metastatic breast cancer succumb to their disease. One particular place that metastatic breast cancer does metastasize to is the central nervous system. When central nervous system metastases do occur, the usual treatment is surgery (for a solitary metastasis) or radiation, or surgery plus radiation therapy.

[0011] Lung cancer is reportedly the leading cause of cancer death in men and women. *The Merck Manual* 731 (16<sup>th</sup> ed. 1992). A variety of causes exist, but cigarette smoking accounts for greater than 90 percent of reported cases in men and greater than 70 percent of reported cases in women. Id.

[0012] Most patients with lung cancer present a tumor that has already metastasized to a variety of organs, including lung, liver, adrenal gland and other organs. Treatment of metastatic lung cancer is not yet standardized. Ihde, D.C., *The New England Journal of Medicine* 327:1434-1441 (1992). However, chemotherapy regimens that are utilized include treatment with cisplatin plus etoposide, combinations of cyclophosphamide plus doxorubicin plus cisplatin, and single agents alone or in combination, including ifosfamide, teniposide, vindesine, carboplatin, vincristine, taxol, nitrogen mustard, methotrexate, hexamethylmelamine and others. Despite these chemotherapeutic regimens the average patient with metastatic lung cancer still only survives 7-12 months. One particular troublesome place for metastases of lung cancer is the central nervous system. The treatment for central nervous system metastases includes surgery (to remove a solitary lesion), radiation therapy, or a combination of both.

[0013] Each year about 50,000 new cases of bladder cancer are reported in the United States. *The Merck Manual* 1749 (16<sup>th</sup> ed. 1992). Although at presentation the disease is usually localized, most patients develop distant metastatic disease. The most recent advances have been in the area of chemotherapy for patients with such metastatic disease. One effective regimen is called the MVAC regimen. It consists of treatment with methotrexate plus vinblastine plus adriamycin (doxorubicin) plus cisplatin. Although the response rate is high to this chemotherapeutic regimen, medical oncologists are noting that one place the patients fail is with metastases to the central nervous system.

[0014] It is estimated that more than 120,000 men will be diagnosed with prostate cancer this year. *The Merck Manual* 1750 (16<sup>th</sup> ed. 1992). The most common sites of metastases in patients with prostate cancer are the bone and lymph nodes. The bone metastases are particularly bothersome in that they can create intense pain for the patient. The current treatment for metastatic prostate cancer includes treatment with flutamide, leuprolide, diethylstilbestrol, and other hormonal manipulations, as well as chemotherapy (doxorubicin, estramustine phosphate, vinblastine, suramin, cisplatin, and others). Unfortunately, none of these agents are consistently helpful in the disease. In addition, as patients with prostate cancer live longer with their malignancy, they will most likely develop a higher incidence of metastases to the central nervous system (including the spinal cord).

## 2.5. ESOPHAGEAL CANCER

[0015] Several years ago, carcinoma of the esophagus reportedly represented only about six percent of all cancers of the gastrointestinal tract; however, it reportedly caused a disproportionate number of cancer deaths. Boring, C. C., et al., *CA Cancer J. Clin.* 43:7 (1993). These cancers usually arise from the epithelial layer of the esophagus and are either squamous cell carcinomas or adenocarcinomas. Overall, the 5 year survival is about five percent.

## 2.6. LEUKEMIA

[0016] Leukemia refers to malignant neoplasms of the blood-forming tissues. Although viruses reportedly cause several forms of leukemia in animals, causes of leukemia in humans are to a large extent unknown. *The Merck Manual* 1233 (16<sup>th</sup> ed. 1992). Transformation to malignancy typi-

cally occurs in a single cell through two or more steps with subsequent proliferation and clonal expansion. In some leukemias, specific chromosomal translocations have been identified with consistent leukemic cell morphology and special clinical features (e.g., translocations of 9 and 22 in chronic myelocytic leukemia, and of 15 and 17 in acute promyelocytic leukemia). Acute leukemias are predominantly undifferentiated cell populations and chronic leukemias more mature cell forms.

[0017] Acute leukemias are divided into lymphoblastic (ALL) and non-lymphoblastic (ANLL) types. They may be further subdivided by their morphologic and cytochemical appearance according to the French-American-British (FAB) classification or according to their type and degree of differentiation. The use of specific B- and T-cell and myeloid-antigen monoclonal antibodies are most helpful for classification. ALL is predominantly a childhood disease which is established by laboratory findings and bone marrow examination. ANLL, also known as acute myeloblastic leukemia (AML), occurs at all ages and is the more common acute leukemia among adults; it is the form usually associated with irradiation as a causative agent.

[0018] Chronic leukemias are described as being lymphocytic (CLL) or myelocytic (CML). CLL is characterized by the appearance of mature lymphocytes in blood, bone marrow, and lymphoid organs. The hallmark of CLL is sustained, absolute lymphocytosis ( $>5,000/\mu\text{L}$ ) and an increase of lymphocytes in the bone marrow. Most CLL patients also have clonal expansion of lymphocytes with B-cell characteristics. CLL is a disease of older persons. In CML, the characteristic feature is the predominance of granulocytic cells of all stages of differentiation in blood, bone marrow, liver, spleen, and other organs. In the symptomatic patient at diagnosis the total WBC count is usually about  $200,000/\mu\text{L}$ , but may reach  $1,000,000/\mu\text{L}$ . CML is relatively easy to diagnose because of the presence of the Philadelphia chromosome.

[0019] The very nature of hematopoietic cancer necessitates using systemic chemotherapy as the primary treatment modality, and radiation therapy may be used as an adjunct to treat local accumulations of leukemic cells. Surgery is rarely indicated as a primary treatment modality, but may be used in managing some complications. Bone marrow transplantation from an HLA-matched sibling is sometimes indicated.

## 2.7. COLORECTAL CANCERS

[0020] In 1999, the incidence of colorectal cancer in the United States was 129,400 cases. In Western countries, cancers of the colon and rectum account for more new cases of cancer than those of any other anatomic site except the lung. *The Merck Manual* 852 (16<sup>th</sup> ed. 1992). Most colorectal cancers are adenocarcinomas.

[0021] Despite the enormous number of deaths attributed to colorectal cancers, their specific mechanism remains unknown. It is known, however, that cancers of the colon and rectum spread in at least five ways: directed extension through the bowel wall; hematogenous metastases; regional lymph node metastases; perineural spread; and intraluminal metastases. Id.

[0022] Primary treatment of colorectal cancers typically includes surgery. Many patients, however, must also be

treated with a combination of radiation and chemotherapy. As of 1992, the most effective chemotherapy regime consisted of the administration of 5-fluorouracil (5FU) and methyl-CCNU. Id.

## 2.8. TOPOISOMERASE INHIBITORS

[0023] Topoisomerases are enzymes that catalyze the relaxation of negatively supercoiled deoxyribonucleic acid (DNA). The process they catalyze is believed to comprise three steps: cleavage of one or both strands of a supercoiled DNA; passage of a segment of DNA through the break that is formed; and resealing of the break. Type I topoisomerases cleave one strand of DNA; type II topoisomerases cleave both strands. Stryer, L., *Biochemistry* 662-663 (3<sup>rd</sup> ed., 1988).

[0024] Because supercoiled double-stranded DNA must be unwound before processes such as replication, recombination, and transcription can occur, inhibition of the unwinding process can have dramatic consequences. For example, compounds that prevent or slow topoisomerase activity can be used to prevent cell growth and/or cause cell death. Such compounds, which are referred to as "topoisomerase inhibitors," have thus shown promise in the treatment of various types of cancer. Camptothecin and its analogues are examples of topoisomerase inhibitors that exert their effect by stabilizing DNA-topoisomerase I complexes, thereby leaving an irreversible break in the double-stranded DNA with which they are associated. Avgeropoulos, N. G., and Batchelor, T. T., *The Oncologist* 4:209-224 (1999).

[0025] A specific camptothecin analogue is irinotecan (also referred to as CPT-11), which is chemically named (4S)-4,11 -diethyl-4-hydroxy-9-[(4-piperidino-piperidino)carbonyl-oxy]1H-pyranol-[3',4':6,7]indolizino[1,2-b]quinoline-3,14-(4H,12H)dione and is described in U.S. Pat. No. 4,604,463. The hydrochloride trihydrate of irinotecan is sold under the tradename CAMPTOSAR®, and is indicated in the United States for the treatment of patients with metastatic carcinoma of the colon or rectum that recurred or progressed following 5-fluorouracil based therapy. *Physicians' Desk Reference*, 2412-2418 (54<sup>th</sup> ed., 2000). It has also recently been approved in the United States as a first-line therapy to treat patients with metastatic colorectal cancer in combination with 5-fluorouracil and leucovorin. Irinotecan has also reportedly been used to treat other cancers, such as malignant gliomas and NSCLC. See, e.g., Avgeropoulos, N. G., and Batchelor, T. T., *The Oncologist* 4:209-224 (1999).

[0026] Like other topoisomerase inhibitors, irinotecan and its metabolites (e.g., SN-38) have numerous adverse effects. Examples of such adverse effects include, but are not limited to, early and late-forming diarrhea, nausea, vomiting, anorexia, constipation, flatulence, leukopenia, anemia, neutropenia, asthenia, abdominal cramping, fever, pain, loss of body weight, dehydration, alopecia, dyspnea, insomnia, and dizziness. See, e.g., *Physicians' Desk Reference*, 2415 (54<sup>th</sup> ed., 2000). The mechanisms by which these undesired effects occur are not well understood, but are believed to be different. In particular, the early and late-forms of diarrhea typically experienced by patients are reportedly mediated by different mechanisms. Id. But whatever their cause, the severity of one or more of their adverse effects limits the amount of topoisomerase inhibitors that can be administered

to patients. The effectiveness of topoisomerase inhibitors such as irinotecan is consequently limited not only by their ability to inhibit topoisomerase activity, but also by the severity and nature of their adverse effects.

[0027] Attempts have been made to alleviate adverse effects associated with irinotecan. For example, loperamide and the combination of loperamide and acetorphan have reportedly been administered to patients in an effort to reduce delayed-onset diarrhea. Rothenberg, M. L., *Annals of Oncology* 8:837-855 (1997). Unfortunately, these attempts met with limited success. Id.

## 2.9. THALIDOMIDE

[0028] Thalidomide is a racemic compound sold under the tradename THALOMID® and chemically named  $\alpha$ -(N-phthalimido)glutarimide or 2-(2,6-dioxo-3-piperidinyl)-1H-isindole-1,3(2H)-dione. Thalidomide was originally developed in the 1950's to treat morning sickness, but due to its tetragenic effects was withdrawn from use. Thalidomide is now indicated in the United States for the acute treatment of the cutaneous manifestations of erythema nodosum leprosum. *Physicians' Desk Reference*, 911-916 (54<sup>th</sup> ed., 2000). Because its administration to pregnant women can cause birth defects, the sale of thalidomide is strictly controlled. Id.

[0029] In addition to treating symptoms of leprosy, thalidomide has reportedly been used to treat chronic graft-vs-host disease, rheumatoid arthritis, sarcoidosis, several inflammatory skin diseases, and inflammatory bowel disease. See generally, Koch, H. P., *Prog. Med. Chem.* 22:165-242 (1985). See also, Moller, D. R., et al., *J. Immunol.* 159:5157-5161 (1997); Vasiliauskas, E. A., et al., *Gastroenterology* 117:1278-1287 (1999); and Ehrenpreis, E. D., et al., *Gastroenterology* 117:1271-1277 (1999). It has further been alleged that thalidomide can be combined with other drugs to treat ischemia/reperfusion associated with coronary and cerebral occlusion. See U.S. Pat. No. 5,643,915, which is incorporated herein by reference.

[0030] Thalidomide has also reportedly been clinically investigated in the treatment of specific types of cancers. These include refractory multiple myeloma, brain, melanoma, breast, colon, mesothelioma, and renal cell carcinoma. See, e.g., Singhal, S., et al., *New England J. Med.* 341(21):1565-1571 (1999); and Marx, G. M., et al., *Proc. Am. Soc. Clin. Oncology* 18:454a (1999). It has further been reported that thalidomide can be used to prevent the development of chronic cardiomyopathy in rats caused by doxorubicin. Costa, P. T., et al., *Blood* 92(10:suppl. 1):235b (1998). Other reports concerning the use of thalidomide in the treatment of specific cancers include its combination with carboplatin in the treatment of glioblastoma multiforme. McCann, J., *Drug Topics* 41-42 (Jun. 21, 1999). Thalidomide has reportedly also been used as an antiemetic during the treatment of astrocytoma. Zwart, D., *Arzneim.-Forsch.* 16(12):1688-1689 (1966).

[0031] If there is a general mechanism by which thalidomide aids in the treatment of some cancers, its nature remains unclear. See, e.g., Moreira, A. L., et al., *J. Exper. Med.* 177:1675-1680 (1993); McHugh, S. M., et al., *Clin. Exper. Immunol.* 99:160-167 (1995); and Moller, D. R., et al., *J. Immunol.* 159:5157-5161 (1997). It has been reported, however, that thalidomide is an antiangiogenic agent that can suppress tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and interleu-



kin 12 (IL-12) production. See, e.g., Moller, D. R., et al., *J. Immunol.* 159:5157-5161 (1997); Moreira, A. L., et al., *J. Exp. Med.* 177:1675-1680 (1993); U.S. Pat. Nos. 5,593,990, 5,629,327, and 5,712,291 to D'Amato and U.S. Pat. No. 5,385,901 to Kaplan. And in vitro studies suggest that thalidomide affects the production of a variety of other proteins. See, e.g., McHugh, S. M., et al., *Clin. Exp. Immunol.* 99:160-167 (1995). Thalidomide may also affect mechanisms related to epithelial or endothelial function or growth. D'Amato M., et al., *Proc. Natl. Acad. Sci.* 91:4082-4085(1994).

[0032] Given the great need for an effective and safe treatment of cancer, there continues to be an extensive amount of research on new drugs or ways of improving existing therapies. This invention addresses the need for a safe and effective cancer treatment.

### 3. SUMMARY OF THE INVENTION

[0033] This invention is directed to pharmaceutical compositions, pharmaceutical dosage forms, kits, methods of treating or preventing cancer, methods of reducing or avoiding adverse effects associated with chemotherapy and radiation therapy, and methods of improving the tolerance of patients to chemotherapy and radiation treatment.

[0034] A first embodiment of the invention encompasses a method of treating primary and/or metastatic cancer, which comprises administering to a patient in need of such treatment a therapeutically effective amount of a topoisomerase inhibitor, or a pharmaceutically acceptable prodrug, salt, solvate, hydrate, or clathrate thereof, and a therapeutically effective amount of thalidomide, or a pharmaceutically acceptable prodrug, salt, solvate, hydrate, or clathrate thereof.

[0035] Specific examples of cancers that can be treated by this method include, but are not limited to, cancer of the head, neck, eye, mouth, throat, esophagus, chest, bone, lung, colon, rectum, stomach, prostate, breast, ovaries, kidney, liver, pancreas, and brain. A specific cancer that can be treated by this method is metastatic colorectal cancer.

[0036] A second embodiment of the invention encompasses a method of increasing the dosage of a topoisomerase inhibitor that can be safely and effectively administered to a patient, which comprises administering to a patient in need of such an increased dosage an amount of thalidomide, or a pharmaceutically acceptable prodrug, salt, solvate, hydrate, or clathrate thereof, that is sufficient to reduce a dose-limiting adverse effect associated with the topoisomerase inhibitor. In a preferred method of this embodiment, thalidomide is administered orally and daily in an amount of from about 1 to about 2000 mg, preferably from about 50 to about 1000 mg, more preferably from about 100 to 750 mg, and most preferably from about 200 to about 500 mg.

[0037] Examples of dose-limiting adverse effects associated with topoisomerase inhibitors include, but are not limited to: gastrointestinal toxicity such as, but not limited to, early and late-forming diarrhea and flatulence; nausea; vomiting; anorexia; leukopenia; anemia; neutropenia; asthenia; abdominal cramping; fever; pain; loss of body weight; dehydration; alopecia; dyspnea; insomnia; dizziness, mucositis, xerostomia, and kidney failure. Specific dose-limiting adverse effects are early-forming diarrhea and late-forming diarrhea.

[0038] A third embodiment of the invention encompasses a method of reducing or preventing an adverse effect associated with chemotherapy or radiation therapy, which comprises administering to a patient in need of such treatment or prevention an amount of thalidomide, or a pharmaceutically acceptable prodrug, salt, solvate, hydrate, or clathrate thereof, that is sufficient to reduce an adverse effect associated with the chemotherapy or radiation therapy. This embodiment includes the use of thalidomide to protect against or treat an adverse effect associated with the use of chemotherapy or radiation therapy. The use of the thalidomide in this embodiment encompasses raising a patient's tolerance for chemotherapy or radiation therapy. In a preferred method of this embodiment, thalidomide is administered orally and daily in an amount of from about 1 to about 2000 mg, preferably from about 50 to about 1000 mg, more preferably from about 100 to 750 mg, and most preferably from about 200 to about 500 mg.

[0039] Examples of adverse effects associated with chemotherapy and radiation therapy include, but are not limited to: gastrointestinal toxicity such as, but not limited to, early and late-forming diarrhea and flatulence; nausea; vomiting; anorexia; leukopenia; anemia; neutropenia; asthenia; abdominal cramping; fever; pain; loss of body weight; dehydration; alopecia; dyspnea; insomnia; dizziness, mucositis, xerostomia, and kidney failure.

[0040] A fourth embodiment of the invention encompasses a method of increasing the therapeutic efficacy of a topoisomerase inhibitor which comprises administering to a patient in need of such increased therapeutic efficacy an amount of thalidomide, or a pharmaceutically acceptable prodrug, salt, solvate, hydrate, or clathrate thereof, that is sufficient to increase the therapeutic efficacy of the topoisomerase inhibitor.

[0041] A fifth embodiment of the invention encompasses a pharmaceutical composition comprising a topoisomerase inhibitor, or a pharmaceutically acceptable prodrug, salt, solvate, hydrate, or clathrate thereof, and thalidomide, or a pharmaceutically acceptable prodrug, salt, solvate, hydrate, or clathrate thereof.

[0042] A sixth embodiment of the invention encompasses a dosage form comprising a topoisomerase inhibitor, or a pharmaceutically acceptable prodrug, salt, solvate, hydrate, or clathrate thereof, and thalidomide, or a pharmaceutically acceptable prodrug, salt, solvate, hydrate, or clathrate thereof.

[0043] A seventh embodiment of the invention encompasses a kit for use in the treatment or prevention of cancer which comprises a parenteral dosage form of irinotecan, or a pharmaceutically acceptable prodrug, salt, solvate, hydrate, or clathrate thereof, and an oral dosage form of thalidomide, or a pharmaceutically acceptable prodrug, salt, solvate, hydrate, or clathrate thereof.

[0044] Examples of topoisomerase inhibitors that can be used in the methods, compositions, and kits of the invention include, but are not limited to, camptothecin, irinotecan, SN-38, topotecan, 9-aminocamptothecin, GG-211, DX-8951f, saintopin, UCE6, UCE1022, TAN-1518A, TAN-1518B, KT6006, KT6528, ED-110, NB-506, ED-110, NB-506, rebeccamycin, bulgarein, Hoechst dye 33342, Hoechst dye 33258, nitidine, fagaranine, epiberberine, cora-

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