THERAPEUTIC CANCER TREATMENTS

BACKGROUND

Hedgehog signaling is essential in many stages of development, especially in formation of left-right symmetry. Loss or reduction of hedgehog signaling leads to multiple developmental deficits and malformations, one of the most striking of which is cyclopia.

Many tumors and proliferative conditions have been shown to depend on the hedgehog pathway. The growth of such cells and survival can be affected by treatment with the compounds disclosed herein. Recently, it has been reported that activating hedgehog pathway mutations occur in sporadic basal cell carcinoma (Xie *et al.* (1998) Nature 391: 90-92) and primitive neuroectodermal tumors of the central nervous system (Reifenberger *et al.* (1998) Cancer Res 58: 1798-803). Uncontrolled activation of the hedgehog pathway has also been shown in numerous cancer types such as GI tract cancers including pancreatic, esophageal, gastric cancer (Berman *et al.* (2003) Nature 425: 846-51, Thayer *et al.* (2003) Nature 425: 851-56) lung cancer (Watkins *et al.* (2003) Nature 422: 313-317, prostate cancer (Karhadkar *et al* (2004) Nature 431: 707-12, Sheng *et al.* (2004) Molecular Cancer 3: 29-42, Fan *et al.* (2004) Endocrinology 145: 3961-70), breast cancer (Kubo *et al.* (2004) Cancer Research 64: 6071-74, Lewis *et al.* (2004) Journal of Mammary Gland Biology and Neoplasia 2: 165-181) and hepatocellular cancer (Sicklick *et al.* (2005) ASCO conference, Mohini *et al.* (2005) AACR conference).

For example, small molecule inhibition of the hedgehog pathway has been shown to inhibit the growth of basal cell carcinoma (Williams, *et al.*, 2003 PNAS 100: 4616-21), medulloblastoma (Berman *et al.*, 2002 Science 297: 1559-61), pancreatic cancer (Berman *et al.*, 2003 Nature 425: 846-51), gastrointestinal cancers (Berman *et al.*, 2003 Nature 425: 846-51, published PCT application WO 05/013800), esophageal cancer (Berman *et al.*, 2003 Nature 425: 846-51), lung cancer (Watkins *et al.*, 2003. Nature 422: 313-7), and prostate cancer (Karhadkar *et al.*, 2004. Nature 431: 707-12).

In addition, it has been shown that many cancer types have uncontrolled activation of the hedgehog pathway, for example, breast cancer (Kubo *et al.*, 2004. Cancer Research 64: 6071-4), hepatocellular cancer (Patil *et al.*, 2005. 96th Annual AACR conference, abstract #2942 Sicklick *et al.*, 2005. ASCO annual meeting, abstract #9610), hematological malignancies (Watkins and Matsui, unpublished results), basal cell carcinoma (Bale & Yu,

2001. Human Molec. Genet. 10:757-762 Xie *et al*., 1998 Nature 391: 90-92), medulloblastoma (Pietsch *et al*., 1997. Cancer Res. 57: 2085-88), prostate cancer (Karhadkar et al., 2003, Nature, 431:846-851), and gastric cancer (Ma *et al*., 2005 Carcinogenesis May 19, 2005 (Epub)).

SUMMARY

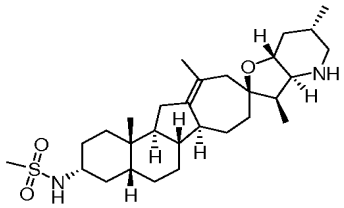
The invention relates generally to methods of extending relapse free survival in a cancer patient who is undergoing treatment with a chemotherapeutic, by administering a therapeutically effective amount of a hedgehog inhibitor to the patient. In some embodiments, the hedgehog inhibitor is administered concurrently with the chemotherapeutic. In instances of concurrent therapy, the hedgehog inhibitor may continue to be administered after treatment with the chemotherapeutic has ceased. In other embodiments, the hedgehog inhibitor is administered after treatment with the chemotherapeutic has ceased (i.e., sequential treatment with no period of concurrent treatment with the chemotherapeutic).

In another embodiment, the invention relates to a method of extending relapse free survival in a cancer patient who had previously been treated with a chemotherapeutic, by administering a therapeutically effective amount of a hedgehog inhibitor to the patient after treatment with the chemotherapeutic has ceased.

The cancer treated by the methods described herein can be selected from, for example, lung cancer (e.g., small cell lung cancer or non-small cell lung cancer), bladder cancer, ovarian cancer, and colon cancer. For treatment of small cell lung cancer according to the invention, the chemotherapeutic can be selected from etoposide, carboplatin, cisplatin, irinotecan, topotecan, gemcitabine, radiation therapy, and combinations thereof. An example of suitable chemotherapeutics for treatment of non-small cell lung cancer according to the invention include vinorelbine; cisplatin; docetaxel; pemetrexed; etoposide; gemcitabine; carboplatin; targeted therapies including bevacizumab, gefitinib, erlotinib, and cetuximab; radiation therapy; and combinations thereof. For treatment of bladder cancer according to the invention, suitable chemotherapeutics include gemcitabine, cisplatin, methotrexate, vinblastin, doxorubicin, paclitaxel, docetaxel, pemetrexed, mitomycin C, 5-fluorouracil, radiation therapy, and combinations thereof. Examples of suitable chemotherapeutics for the treatment of ovarian cancer according to the invention include

paclitaxel; docetaxel; carboplatin; gemcitabine; doxorubicin; topotecan; cisplatin; irinotecan; targeted therapies such as bevacizumab; radiation therapy; and combinations thereof. For treatment of colon cancer according to the invention, examples of suitable chemotherapeutics include paclitaxel; 5-fluorouracil; leucovorin; irinotecan; oxaliplatin; capecitabine; targeted therapies including bevacizumab, cetuximab, and panitumumab; radiation therapy; and combinations thereof.

An example of a suitable hedgehog inhibitor is a compound of formula I:

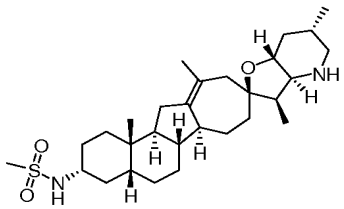


I

or a pharmaceutically acceptable salt thereof. An example of a pharmaceutically acceptable salt of the compound of formula I is a hydrochloride salt.

In some embodiments, the hedgehog inhibitor is administered as a pharmaceutical composition comprising the hedgehog inhibitor, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In another embodiment, the invention relates to a method of treating pancreatic cancer, by administering to a patient in need thereof a therapeutically effective amount of a compound of formula I:



I

or a pharmaceutically acceptable salt thereof. An example of a therapeutically acceptable salt of the compound of formula I is a hydrochloride salt. The method can also include administration of the compound of formula I, or a pharmaceutically acceptable salt thereof, in combination with a chemotherapeutic (e.g., gemcitabine). Administration of the compound of formula I can continue after treatment with the chemotherapeutic has ceased. The compound of formula I can administered as a pharmaceutical composition comprising

the compound of formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

DETAILED DESCRIPTION

The invention relates to methods for treating various conditions and disorders, by administering hedgehog inhibitors. In some instances, the hedgehog inhibitor is administered in combination with other therapies, including other chemotherapeutics. The hedgehog inhibitor can be administered concurrently, sequentially, or a combination of concurrent administration followed by monotherapy with the hedgehog inhibitor.

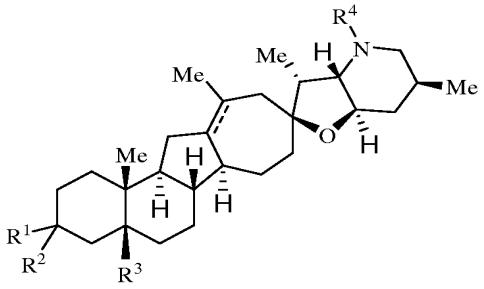
In one aspect, the invention relates to a method of treating cancer. The method includes administering to a patient a first therapeutic agent, and a second therapeutic agent, wherein the second therapeutic agent is a hedgehog inhibitor. The two agents can be administered concurrently (i.e., essentially at the same time, or within the same treatment) or sequentially (i.e., one immediately following the other, or alternatively, with a gap in between administration of the two). In some embodiments, the hedgehog inhibitor is administered after the first therapeutic. The first therapeutic agent can be a chemotherapeutic agent, such as etoposide, carboplatin, or a combination thereof.

In another aspect, the invention relates to a method of treating cancer. The method includes the steps of: administering to a patient a first therapeutic agent; then administering the first therapeutic agent in combination with a second therapeutic agent, wherein said second therapeutic agent is a hedgehog inhibitor. Specific examples of conditions that can be treated include lung cancer (e.g., small cell lung cancer, non-small cell lung cancer).

In another aspect, the invention relates to a method of treating a condition mediated by the hedgehog pathway. The method includes administering to a patient a first therapeutic agent, and a second therapeutic agent, where said second therapeutic agent is a hedgehog inhibitor. In some embodiments, the method includes the steps of: (1) administering to a patient a first therapeutic agent; then (2) administering the first therapeutic agent in combination with a second therapeutic agent, where the second therapeutic agent is a hedgehog inhibitor. The first agent can be a chemotherapeutic agent.

Suitable hedgehog inhibitors include, for example, those described and disclosed in U.S. Patent 7,230,004 and U.S. Patent Application Publication 2008/0293754, the entire disclosures of which are incorporated by reference herein.

For example, the hedgehog inhibitor can be a compound having the following structure:



or a pharmaceutically acceptable salt thereof; wherein

R^1 is H, alkyl, -OR, amino, sulfonamido, sulfamido, $-OC(O)R^5$, $-N(R^5)C(O)R^5$, or a sugar;

R^2 is H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, nitrile, or heterocycloalkyl;

or R^1 and R^2 taken together form =O, =S, =N(OR), =N(R), $=N(NR_2)$, or $=C(R)_2$;

R^3 is H, alkyl, alkenyl, or alkynyl;

R^4 is H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaryl, heteroaralkyl, haloalkyl, -OR, $-C(O)R^5$, $-CO_2R^5$, $-SO_2R^5$, $-C(O)N(R^5)(R^5)$, $-[C(R)_2]_q-R^5$, $-[(W)-N(R)C(O)]_qR^5$, $-[(W)-C(O)]_qR^5$, $-[(W)-C(O)O]_qR^5$, $-[(W)-OC(O)]_qR^5$, $-[(W)-SO_2]_qR^5$, $-[(W)-N(R^5)SO_2]_qR^5$, $-[(W)-C(O)N(R^5)]_qR^5$, $-[(W)-O]_qR^5$, $-[(W)-N(R)]_qR^5$, $-W-NR_3^+X^-$ or $-[(W)-S]_qR^5$;

each W is independently for each occurrence a diradical;

each q is independently for each occurrence 1, 2, 3, 4, 5, or 6;

X^- is a halide;

each R^5 is independently for each occurrence H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, aralkyl, heteroaryl, heteroaralkyl or $-[C(R)_2]_p-R^6$;

or any two occurrences of R^5 on the same substituent can be taken together to form a 4-8 membered optionally substituted ring which contains 0-3 heteroatoms selected from N, O, S, and P;

p is 0-6;

each R^6 is independently hydroxyl, -N(R)COR, -N(R)C(O)OR, $-N(R)SO_2(R)$, $-C(O)N(R)_2$, $-OC(O)N(R)(R)$, $-SO_2N(R)(R)$, -N(R)(R), -COOR, -C(O)N(OH)(R), $-OS(O)_2OR$, $-S(O)_2OR$, -OP(O)(OR)(OR), -NP(O)(OR)(OR), or -P(O)(OR)(OR);

provided that when R^2, R^3 are H and R^4 is hydroxyl; R^1 can not be hydroxyl;

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