NICLOSAMIDE AND ITS DERIVATIVES FOR USE IN THE TREATMENT OF SOLID TUMORS

The present invention relates to novel therapeutic uses of niclosamide for the treatment of cancer. In particular, a combination of niclosamide or one of its derivatives with an alkylating agent is provided for the treatment of solid tumors. Moreover, niclosamide or one of its derivatives can be used for the treatment of solid tumors characterized by underexpression of NFKBIA. Finally, the invention relates to diagnostic methods for determining whether treatment with niclosamide alone or in combination with an alkylating agent is suitable for a cancer patient.

Background of the Invention

Chemotherapy has developed to an increasingly effective line of defense against cancer (1). In glioblastoma (GBM), the alkylating agent temozolomide (TMZ) has become a standard, in combination with surgical resection and radiotherapy. There is nevertheless a considerable need to develop alternative treatment options, as GBM remains a fatal disease with a median overall survival of only 15 months (2, 3). For anticancer drug discovery, two major strategies are traditionally employed (4). One is the targeted approach where cancer-related molecules and/or signaling cascades need to be exposed before specific compounds can be designed for distinct interference and inhibition. Alternatively, empirical screening of hundreds to thousands of compounds can be conducted to identify otherwise unpredictable antineoplastic effects. Both strategies, however, are burdened with high attrition rates during clinical translation (5, 6). This may in part be caused by the use of inept cellular model systems for drug evaluation at early developmental stages (7), e.g. inter- and intra-patient tumor heterogeneity is rarely reflected within these systems. The present inventors have developed an *in vitro* cellular system that is closely mirroring GBM in vivo and is, thus, particular suitable to identify compounds and combinations of compounds that are likely to also provide GBM specific anticancer activity when used in vivo. Using this in vitro cellular system the present inventors were able to identify compounds and compound combinations for the improved chemotherapy of glioblastoma.

Summary ~~of the Invention~~

In a first aspect the invention relates to use of a cytostatic compound and an alkylating compound in the manufacture of a medicament for the treatment of glioblastoma, wherein the cytostatic compound is niclosamide, and wherein the alkylating compound is temozolomide. In another aspect, the present invention refers to use of a cytostatic compound in the manufacture of

a medicament for the treatment of a glioblastoma characterized by a decreased expression level of NFKBIA, wherein the cytostatic compound is niclosamide. Also disclosed herein is a combination of a first cytostatic compound according to formula I, II or III

R_6 if present is hydrogen or C_1 to C_6 alkyl;

R_9 is nitro, hydrogen, hydroxyl, amino, halogen, alkyl, alkenyl, alkynyl, or aryl; and

R_{21}, R_{22}, R_{23}, and R_{24}, if present are independently hydrogen, hydroxyl, halogen, alkyl, alkenyl, alkynyl, cycloalkyl or aryl;

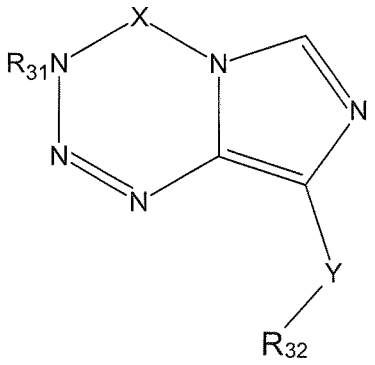
R_{25} and R_{26} if present are independently hydrogen, hydroxyl, halogen, alkyl, alkenyl, alkynyl, cycloalkyl or aryl; and

R_{27} if present is hydrogen or C_1 to C_6 alkyl;

or salt thereof;

and an alkylating compound for use in treating of a solid tumor.

In ~~an aspect of the invention~~one example, the alkylating compound has a structure according to formula IV



(IV)

wherein

X and Y are independently carbonyl, methylene, hydroxymethinyl, alkoxymethinyl, aminomethinyl, oxime, hydrazone, arylhydrazone or semicarbazone,

R_{31} is hydrogen, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl or aryl; and

R_{32} is amino, hydrogen, hydroxyl or halogen

or salt thereof.

In a further ~~aspect~~example, ~~the present invention relates to~~disclosed herein is a pharmaceutical composition comprising a compound according to formula I, II or III, wherein A, B, R_1 to R_{11} and R_{21} to R_{24} have a meaning as defined above, an alkylating agent and a pharmaceutically acceptable excipient for use in treating of a solid tumor.

In yet a further ~~aspect~~example, disclosed herein is~~the present invention relates to~~ a compound according to formula I, II or III, wherein A, B, R_1 to R_{11} and R_{21} to R_{24} have a meaning as defined above for use in treating a

solid tumor characterized by a decreased expression level NFKBIA.

In yet a further ~~aspect~~example, disclosed herein is~~the present invention relates to~~ a method for determining if therapy with the cytostatic compound according to formula I, II or III as defined supra is suitable for treating a patient with a solid tumor comprising the steps of

a) determining the expression level of NFKBIA in a sample of tumor cells or tumor tissue of the patient;

b) comparing the determined expression level with a reference value;

c) determining if the therapy with niclosamide is suitable for the patient based on the result of the comparison of step b), wherein underexpression or a deletion of NFKBIA indicates that the combination therapy is suitable for the patient.

In yet another ~~aspect~~example, disclosed herein is~~the present invention relates to~~ a method for determining the molar ratio of niclosamide to temozolomide to be administered to a patient with a solid tumor comprising the steps of

a) determining the expression level of NFKBIA in a sample of tumor cells or tumor tissue of the patient;

b) comparing the determined expression level with a reference value;

c) determining the molar ratio of niclosamide to temozolomide based on the result of the comparison of step b), wherein

(i) an expression above the reference value indicates that the molar ratio shall be below 40 % niclosamide; and

(ii) an expression level below the reference value indicates that the molar ratio shall be larger than or equal to 40 % niclosamide.

Detailed Description of the Invention

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art.

Preferably, the terms used herein are defined as described in "A multilingual glossary of biotechnological terms: (IUPAC Recommendations)", Leuenberger, H.G.W, Nagel, B. and Klbl, H. eds. (1995), Helvetica Chimica Acta, CH-4010 Basel, Switzerland).

Throughout this specification and the claims which follow, unless the context requires otherwise,

Claims

1. Use of a cytostatic compound and an alkylating compound in the manufacture of a medicament for the treatment of glioblastoma, wherein the cytostatic compound is niclosamide, and wherein the alkylating compound is temozolomide.

2. The use of claim 1, wherein the molar ratio between niclosamide and temozolomide is in the range of 10% niclosamide/90% temozolomide to 90% niclosamide/10% temozolomide.

3. The use of claim 1 or 2, wherein the glioblastoma is primary glioblastoma, de novo glioblastoma; secondary glioblastoma; recurrent glioblastoma, glioblastoma with increased methylation of the promoter of the gene O6-Methylguanin-Methyltransferase (MGMT), glioblastoma without increased methylation of the promoter of MGMT, glioblastoma with mutated p53, glioblastoma without mutated p53, glioblastoma with alterations of the gene encoding kappa light polypeptide gene enhancer in B-cells inhibitor (NFκBIA), glioblastoma without alterations of the gene encoding NFκBIA, glioblastoma with alterations of the gene encoding epidermal growth factor receptor (EGFR), glioblastoma without alterations of the gene encoding EGFR, glioblastoma with alterations of the gene encoding platelet-derived growth factor receptor (PDGFRA), glioblastoma without alterations of the gene encoding PDGFRA, glioblastoma with alterations of the gene encoding isocitrate dehydrogenase 1 (IDHI), glioblastoma without alterations of the gene encoding IDHI, glioblastoma with alterations of the gene encoding neurofibromatosis type 1 (NF1) and glioblastoma without alterations of the gene encoding NF1.

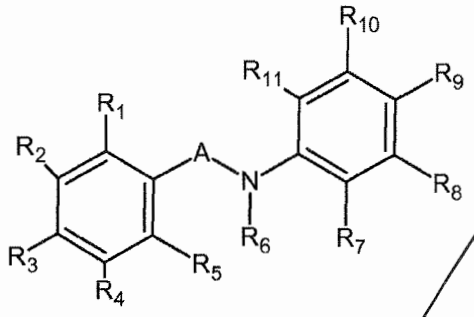
4. The use of any of claims 1 to 3, which are formulated for simultaneous or subsequent administration.

5. The use of claim 4, wherein the formulation for simultaneous administration is a mixture of the two compounds.

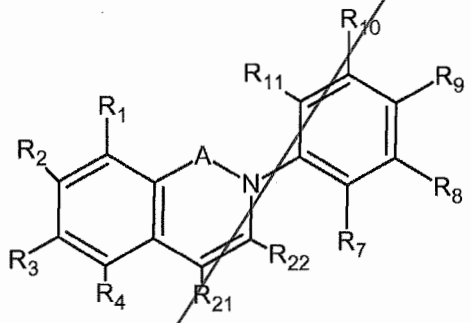
6. Use of a cytostatic compound in the manufacture of a medicament for the treatment of a glioblastoma characterized by a decreased expression level of NFKBIA, wherein the cytostatic compound is niclosamide.

Claims

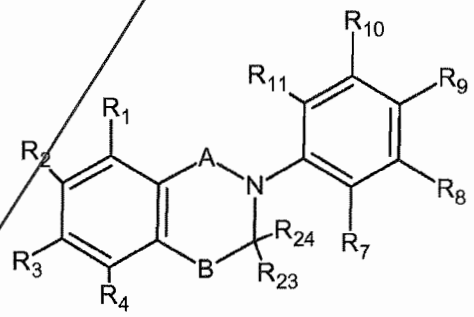
1. A cytostatic compound according to formula I, II or III



(I)



(II)



(III)

wherein

A is carbonyl, methylene, hydroxymethinyl, alkoxymethinyl, aminomethinyl, oxime, hydrazone, arylhydrazone, or semicarbazone;

B if present is $CR_{25}R_{26}$, O, S or NR_{27};

R_1, R_3, R_4, R_8, R_{10}, and R_{11} are independently hydrogen, hydroxyl, alkoxy, halogen or C_1 to C_6 alkyl;

R_2 and R_7 are independently halogen, hydroxyl or hydrogen,

R_5 if present is hydroxyl, phosphate, hydrogen, halogen, alkyl, cycloalykyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio or amino;

R_6 if present is hydrogen or C_1 to C_6 alkyl;

R_9 is nitro, hydrogen, hydroxyl, amino, halogen, alkyl, alkenyl, alkynyl, or aryl; and

R_{21}, R_{22}, R_{23}, and R_{24}, if present are independently hydrogen, hydroxyl, halogen, alkyl, alkenyl, alkynyl, cycloalkyl or aryl;

R_{25} and R_{26} if present are independently hydrogen, hydroxyl, halogen, alkyl, alkenyl, alkynyl, cycloalkyl or aryl; and

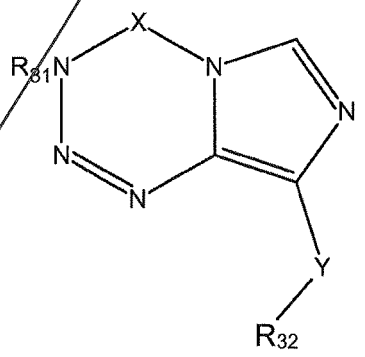
R_{27} if present is hydrogen or C_1 to C_6 alkyl:

or salt thereof;

and an alkylating compound for use in treating of a solid tumor.

2. The compounds of claim 1, wherein the alkylating agent is an O^6-alkylating agent.

3. The compounds of claim 1 or 2, wherein the alkylating compound has a structure according to formula IV



(IV)

wherein

X and Y are independently carbonyl, methylene, hydroxymethinyl, alkoxymethinyl, aminomethinyl, oxime, hydrazone, arylhydrazone or semicarbazone,

R_{31} is alkyl, hydrogen, alkoxy, alkenyl, alkynyl, cycloalkyl or aryl; and

R_{32} is amino, hydrogen, hydroxyl or halogen
or salt thereof.

4. The compounds of any one of claims 1 to 3, wherein the cytostatic compound is niclosamide.

5. The compounds of any one of claims 1 to 4, wherein the alkylating compound is temozolomide.

6. The compounds of claim 4, wherein the molar ratio between niclosamide and temozolomide is in the range of 10% niclosamide/90% temozolomide to 90% niclosamide/10% temozolomide.

7. The compounds of any one of claims 1 to 6, wherein the solid tumor is glioblastoma.

8. The compounds of claim 7, wherein the glioblastoma is primary glioblastoma, de novo glioblastoma; secondary glioblastoma; recurrent glioblastoma, glioblastoma with increased methylation of the promoter of the gene O6-Methylguanin-Methyltransferase (MGMT), glioblastoma without increased methylation of the promoter of MGMT, glioblastoma with mutated p53, glioblastoma without mutated p53, glioblastoma with alterations of the gene encoding kappa light polypeptide gene enhancer in B-cells inhibitor (NFκBIA), glioblastoma without alterations of the gene encoding NFκBIA, glioblastoma with alterations of the gene encoding epidermal growth factor receptor (EGFR), glioblastoma without alterations of the gene encoding EGFR, glioblastoma with alterations of the gene encoding platelet-derived growth factor receptor (PDGFRA), glioblastoma without alterations of the gene encoding PDGFRA, glioblastoma with alterations of the gene encoding isocitrate dehydrogenase 1 (IDHI), glioblastoma without alterations of the gene encoding IDHI, glioblastoma with alterations of the gene encoding neurofibromatosis type 1 (NF1) and glioblastoma without alterations of the gene encoding NF1.

9. The compounds of any of claims 1 to 8, which are formulated for simultaneous or subsequent administration.

10. The compounds of claim 9, wherein the formulation for simultaneous administration is a mixture of the two compounds.

11. The compounds of claims 1 to 10, wherein the cytostatic compound is formulated for resorption into the central nervous system.

12. A pharmaceutical composition comprising the compounds of any of claims 1 to 11 and a pharmaceutically acceptable excipient for use in treating of a solid tumor.

13. A compound according to formula I, II or III, wherein R_1 to R_{11} and R_{21} to R_{27} have the meaning as defined above for use in treating of a solid tumor characterized by a decreased expression level of NFKBIA.

14. A method for determining if therapy with the cytostatic compound according to formula I, II or III as defined in claim 1 is suitable for treating a patient with a solid tumor comprising the steps of

a) determining the expression level of NFκBIA in a sample of tumor cells or tumor tissue of the patient;
b) comparing the determined expression level with a reference value;
c) determining if the therapy with niclosamide is suitable for the patient based on the result of the comparison of step b), wherein underexpression or a deletion of NFκBIA indicates that the combination therapy is suitable for the patient.

15. A method for determining the molar ratio of niclosamide to temozolomide to be administered to a patient with a solid tumor comprising the steps of

a) determining the expression level of NFκBIA in a sample of tumor cells or tumor tissue of the patient;
b) comparing the determined expression level with a reference value;
c) determining the molar ratio of niclosamide to temozolomide based on the result of the comparison of step b), wherein
(i) an expression above the reference value indicates that the molar ratio shall be below 40 % niclosamide; and
(ii) an expression level below the reference value indicates that the molar ratio shall be equal to or larger than 40 % niclosamide.