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(54) Benævnelse: **ANVENDELSE AF NATRIUMMETAARSENIT TIL BEHANDLING AF TUMORER**

(56) Fremdragne publikationer:
EP-A- 0 804 928
WO-A-99/18798
KIM H-S ET AL: "Intracellular Glutathione Level Modulates the Induction of Apoptosis by DELTA-Prostaglandin J2" PROSTAGLANDINS, BUTTERWORTH, STONEHAM, MA, US, vol. 51, no. 6, 1 June 1996 (1996-06-01), pages 413-425, XP004032382 ISSN: 0090-6980
WAXMAN, S., ANDERSON, K.C.: "History of the Development of Arsenic Derivatives in Cancer Therapy" THE ONCOLOGIST, vol. 6, no. 2, 2001, pages 3-10, XP001087583

DESCRIPTION

[0001] The present invention relates to the use of meta-arsenite for the manufacture of a pharmaceutical composition for the treatment of a solid malignancy according to the claims.

[0002] Pharmaceutical compositions containing arsenic are known for cancer therapy. For example, the review by Waxman S. et al (The Oncologist 6(suppl. 2), pp. 3-10 (2001)) describes arsenic disulfide, arsenic trisulfide and arsenic trioxide the use of said composition comprising a salt of meta-arsenite (AsO_2^-) and a pharmaceutically acceptable auxiliary.

[0003] Due to their inherent toxicity, and the advent of good alternatives, interest in arsenic compounds has remained low.

[0004] The object of the present invention is to provide a pharmaceutical composition suitable for use in cancer ther apy, which allows for the treatment of solid tumours. The pharmaceutical composition may be used for treatment of such solid tumours for which currently no treatment exists, or as an alternative or supplementary treatment for such solid tumours.

[0005] To this end, the pharmaceutical composition according to the present invention is characterized in that it is a pharmaceutical composition for the treatment of a solid malignancy chosen from colon tumour, gastric tumour, mammary tumour, ovarian tumour, prostate tumour, and renal tumour, said composition comprising a salt of meta-arsenite (AsO_2^-) and a pharmaceutically acceptable auxiliary.

[0006] It has been found that the specified types of tumour are surprisingly sensitive to the meta-arsenite salt. In the salt the counter-ion of meta-aresenite may be any pharmaceutically acceptable counter-ion.

[0007] In the article by Waxman, mention is made of an ar- . ticle by Tarnowski G.S. et al (Cancer Research, 26(2), pp. 181-206 (1966)) where 8 tumour types were investigated with 14 different anti-tumour chemicals. Potassium arsenite affected only the growth of Ehrlich ascites tumour. Regarding this tumour type it is remarked that it is more sensitive in the ascites than in the sold form. This emphasizes the surprising finding of the present invention.

[0008] According to a preferred embodiment, the salt is an alkaline or earth alkaline metal salt. According to a more preferred embodiment, the alkaline metal salt is a potassium or sodium salt.

[0009] Such salts are readily soluble and are readily available for exerting their anti-tumour effect.

[0010] The invention relates to the use of a salt of meta-arsenite (AsO_2^-) for the manufacture

of a pharmaceutical composition for the treatment of a solid malignancy chosen from colon tumour, gastric tumour, mammary tumour, ovarian tumour, prostate tumour, and renal tumour.

[0011] It was found that solid malignancy belonging to the group consisting of colon tumour, mammary tumour, prostate tumour, and renal tumour were particularly sensitive.

[0012] The present invention will now be elucidated with reference to the following example.

EXAMPLE

[0013] Various human tumor cells were grown at 37°C in a humidified atmosphere (95% air, 5% CO_2) in monolayer cultures in RPMI 1640 medium with phenol red (Life Technologies, Karlsruhe, Germany) supplemented with 10% fetal calf serum. Cells were trypsinized and maintained weekly.

Cytotoxicity assay

[0014] A modified propidium iodide assay (based on W.A. Dengler et. al, Anti-Cancer Drugs, 6, pp. 522-532 (1995)) was used to examine the antiproliferative activity of the study compounds. Briefly, cells will be harvested from exponential phase cultures growing in RPMI 1640 medium supplemented with 10% fetal calf serum by trypsination, counted and plated in 96 well flat-bottomed microtiter plates (140 µl cell suspension, a × 10^4 cells/ml). After a 24h recovery, to allow cells to resume exponential growth, 10 µl culture medium (6 control wells. per plate) or culture medium containing the test drug were added to the wells. Each drug concentration was plated in triplicate. After 4 days of incubation culture medium was replaced by an aqueous propidium iodide solution (6 µg/ml). Microtiter plates were kept at -18°C for 24 h, resulting in a total cell kill. After thawing of the plates, fluorescence was measured using a Millipore Cytofluor 2350-microplate reader (excitation 530 nm, emission 620 nm) in order to quantify the total cell number. The assay included untreated and positive controls (5-FU and vindesine).

[0015] Growth inhibition is expressed as Treated/Control x 100 (or T/C%) . IC_{50} and IC_{70} values were determined by plotting compound concentration versus cell number. Mean IC_{50} and IC_{70} values were calculated according to the formula:

$$\text{Mean } IC_{50,70} = \frac{\sum_{x=1}^{n} \log (IC_{50,70})_x}{10^n}$$

[0016] With x = specific tumor cell line and n = total number of cell lines studied. If IC_{50} or IC_{70} could not be determined within the examined dose range, the lowest or highest concentration

studied was used for the calculation.

[0017] Assays were considered valid only if the positive control (5-FU) induced a tumor growth inhibition of T/C <30%' and if vehicle treated control cells had a fluorescence intensity >500 units.

Results

[0018] The results have been summarized in Table I, which shows that in particular tumour cell lines of the type gastric tumour, ovarian tumour, and in particular prostate tumour, mammary tumour, renal and colon tumour were sensitive to the meta-arsenite compound. In comparison, promyelocytic leukaemia, which is known to respond to arsenic trioxide, showed an IC_{70} value of 6.82 µg/ml. Hence, the tumour cells to which the present invention relates are about 2 to 20 times more sensitive to the meta-arsenite compound according to the present invention.

TABLE I

Tumour	cell line	IC_{70} (µg/ml)
Colon	DLD1	0.48
Gastric	GXF251L	3.08
Mammary	MXAF401NL	0.32
Ovarian	OVCAR3	3.02
Prostate	PC3	0.85
Renal	RXF986L	0.63

REFERENCES CITED IN THE DESCRIPTION

Cited references

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Non-patent literature cited in the description

- **WAXMAN S. et al.**The Oncologist, 2001, vol. 6, 23-10 [0002]
- **TARNOWSKI G.S. et al.**Cancer Research, 1966, vol. 26, 2181-206 [0007]
- **DENGLER**Anti-Cancer Drugs, 1995, vol. 6, 522-532 [0014]

PATENTKRAV

1. Anvendelse af natriummetaarsenit (AsO_2^-) til fremstilling af en farmaceutisk sammensætning til behandling af en fast malignitet, der er valgt fra gruppen bestående af kolontumor, mavetumor, mammatumor, ovarietumor, prostatatumor og nyretumor.

2. Anvendelse ifølge krav 1, hvor den faste malignitet er en kolontumor.

3. Anvendelse ifølge krav 1, hvor den faste malignitet er en mavetumor.

4. Anvendelse ifølge krav 1, hvor den faste malignitet er en mammatumor.

5. Anvendelse ifølge krav 1, hvor den faste malignitet er en ovarietumor.

6. Anvendelse ifølge krav 1, hvor den faste malignitet er en prostatatumor.

7. Anvendelse ifølge krav 1, hvor den faste malignitet er en nyretumor.