

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
19 November 2009 (19.11.2009)

PCT

(10) International Publication Number
WO 2009/138094 A1

(51) International Patent Classification:

A61K 38/43 (2006.01) A61K 31/195 (2006.01)
A61K 39/395 (2006.01) A61P 35/00 (2006.01)

MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO,
NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG,
SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG,
US, UZ, VC, VN, ZA, ZM, ZW.

(21) International Application Number:

PCT/EG2008/000017

(84) Designated States (unless otherwise indicated, for every

(22) International Filing Date:

14 May 2008 (14.05.2008)

kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ,
TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,
MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).

(25) Filing Language:

English

(26) Publication Language:

English

(71) Applicant and

(72) Inventor: ABDUL AZIZ, Sherif Salah [EG/EG]; 151
EL Marg, EL Sharkia, Cairo (EG).

Declarations under Rule 4.17:

— of inventorship (Rule 4.17(iv))

Published:

— with international search report (Art. 21(3))

— with amended claims (Art. 19(1))

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,
CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ,
EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR,
KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME,

(54) Title: PHARMACEUTICAL COMPOSITIONS

(57) Abstract: This invention for treatment of patients having lesions from cancer cells depend on replenish depleted intracellular polymerase enzyme, and enhancement the immune cells to attack cancerous cells with aiding of other clonal antibodies.



WO 2009/138094 A1

Pharmaceutical compositions

Technical Field:

Anticancer therapeutic compositions for treatment of liver cancer

Background Art :

The incidence of many forms of cancer is expected to increase with time. For example, liver cancer is the most commonly diagnosed cancer in Egypt as well as a leading cause of cancer death in males and females. It is projected that in 2010 there will be about 2 millions new cases of live cancer diagnosed in Egypt. And great number of deaths caused by liver cancer. Approximately 70% of the patients diagnosed with liver cancer have a form of the disease, which affect the liver. Liver cancer can metastasize to the skeletal system and patients typically die with overwhelming osseous metastatic disease. As yet, there is no effective curative therapy and very little palliative therapy for patients with metastatic disease. The process of tumor cell metastasis requires that cells depart from the primary tumor, invade the basement membrane, traverse through the bloodstream from tumor cell emboli, interact with the vascular endothelium of the target organ, extravasate, and proliferate to form secondary tumor colonies.

It is generally accepted that Hepatitis viruses HCV and HBV the mostly responsible agents for lesions of cancer cell in liver.

This treatment provide a simple type of therapy without need for the others chemotherapy

Like putative anti-cancer drugs which are cytotoxic due to non- specific delivery of the drug resulting in toxic side effects to normal tissues. Therefore, in treating cancer, there is a need for a therapeutic approach that could enhance the established therapeutic qualities of putative anticancer substances while reducing their undesirable toxicity.

Gene therapy is the one of the most recent trail for cancer therapy ,It depends on , and disease to treat a tissues and cells into an individual's genesinsertion of is replaced with a functional allele mutant in which a defective hereditary diseases one. Although the technology is still in its infancy, it has been used with some success. Like using of gene therapy using adenoviral vectors, based upon a fundamental new understanding of the differences between cancerous and normal liver cells. The findings signal a new way to treat cancers that have spread to the liver, such as metastatic cancers of the colon and breast but there is not any enough proving that liver toxicity is not an issue in gene therapy.

Antisense therapy is not strictly a form of gene therapy, but is a genetically-mediated therapy and is often considered together with other methods.

A major advance in the treatment of inoperable liver cancer was the approval of Nexavar by the FDA on November 19, 2007. Nexavar is a 200 mg pill taken by mouth twice a day (2 tablets in the morning and 2 tablets at night on an empty Stomach). It is known as a kinase inhibitor. Nexavar works by interfering with molecules that may be linked to

sending messages to cancer cells and by interfering in the formation of blood vessels that feed the cancer. Nexavar may also cause death of cancer cells. In clinical trials, patients who took Nexavar lived approximately 3 months longer than patients who took a placebo (dummy drug), and the liver tumor grew much slower in the patients taking Nexavar. This result was considered to be so beneficial that the study was discontinued and Nexavar was granted FDA approval.

But we consider Nexavar drug work for a short time to stoppage the cycle of cancer not for ever, also list of side effects, and include fatigue, weight loss, diarrhea and high blood pressure. Some patients developed a rash that consisted of skin shedding especially on their hands and feet; Nexavar is currently undergoing further studies for patients diagnosed with earlier stages only of liver cancer

Enzyme Therapy Pancreatic enzymes as a new model for cancer eradication depend on that pancreas is a very important organ in the prevention of cancer. This is one reason diabetics get cancer more often than people with normal, functioning pancreases. It is theorized that with solid tumors, enzyme therapy slowly works to degrade the cell membranes of cancer cells, reducing growth and making other treatments more effective. Theoretically yes but the true depend on you must firstly understanding the cancer mechanism, not to destructed it only like the action of radiotherapy or the others chemotherapy.

Disclosure of Invention:

The present invention provides a Surprising discovery for liver cancer therapy. It comprises administering a first component, which contains the main regulator factor for the cell to return again to it's normal function and the second one enhance the immune cells to produce antibodies which reflect the level of consciousness of the immune cells for acceptance the power of anti cancer role.

The present invention delivers magic therapeutic agents to a tumor using both targeting and pre-targeting methods to achieve effective and efficient delivery of the agents to the sites. The present invention provides a therapy method that addresses the problem of tumor heterogeneity by using multispecific targeting agents and by delivering at least three different therapeutic agents having different tumor-killing properties to the tumor sites.

The present invention further provides a therapy method that minimizes patient toxicity caused by the therapeutic agents by using pre-targeting and targeting methods of delivery.

The present invention additionally provides a therapy method with no toxic Effects on normal tissue.

The present method of therapy specifically includes the following steps:

(A) administering to the patient a first component which is tag DNA polymerase enzyme, a highly thermos table DNA polymerase of thermophilic bacterium thermus aquaticus

In concentration 5 u/UI, this enzyme is the central enzyme in DNA replication and also serves an important role in DNA repair.

(B) Administering to the patient a second component which is specific monoclonal antibodies for streptolysine antigen (Antistreptolysin Antibodies)

In concentration 800 todd/100 u, where this type of antibodies one of body defense when we infect by streptococcus haemolyticus bacterium antigen (Streptolysin Ag)

(C) Administering to the patients the third component which is tranexamic acid

Which has a good anti fibrinolytic mechanism to stop the process of the inflammation and prevent excessive fibrin degradation, we use it as a diluent for tag DNA polymerase enzyme in concentration 100 mg/1ml.

To apply the present invention specially for HCC of the liver, We depend on mechanism of the viral hepatitis HCV in the liver cells, this virus make the cell go in one direction and applied all orders for the virus with ought refuse, this means the liver cell lose the power of anti –mechanism which make the cell still conscious.

The virus to support this mechanism he depleted all the polymerase activity contents of the cell, so there are marked accumulation for DNA damage and no repair for the DNA to return again for the cell original function. So we hypothesized that if we give the cell another source for polymerase enzyme from biological active bacterium cells, we can restore the damage DNA and solve the problem of DNA fragments accumulation within the cell to return fast to their normal function.

Other mechanism like HCV, we found it but his time in streptococcus haemolyticus bacterium; it secrete large amount of streptolysine antigen to destruct and lyses

Great amount of cell membranes and fibrin to make the inflammation persist for a long time, so this type of bacterium behave the same mechanism of HCV

For this we hypothesized that using the antibodies which our bodies produce as result of attacking by is antigen one of suitable method to stop the process of inflammation which considered the suitable conditions for cancer to grow up.

We combine the three components for treatment of liver cancer to exert the three effects for them.

Materials

Patients with well define focal lesions in the liver right or left lobe or both, splenomegally, ascitis.

Patients with advanced HCC and histologically confirmed cancer. All the patients have been explained to them that they have diagnosis with cancer and you understand that this treatment may increase your chances of living free from cancer.

And we told him about the combination treatment, the idea of the drug and the percentages of succeed, all of them concerning in participation of this study.

The patients conducted to pre treatment evaluations these parameters are a routine part of cancer patients work-up and follow up, complete history and physical examination ,including weight and height with an assessment of the patients performance status, routine laboratory study CBC with differential and platelets ,AFP ,liver enzymes and albumin level

Imaging study chest x-ray, liver C.T and abdominal sonography and satisfactory histological needle aspiration biopsy .

Dosage Regimen

the compositions are preferably administered to an individual in a "therapeutically effective amount", this being sufficient to show benefit to the individual. The actual amount administered, and rate and time-course of administration, will depend on the nature and severity of what is being treated. Prescription of treatment, e.g. decisions on dosage etc, is ultimately within the responsibility and at the discretion of general practitioners and other medical doctors, and typically takes account of the disorder to be treated, the condition of the individual patient, the site of delivery, the method of administration and other factors known to practitioners.

The optimal dose can be determined by physicians based on a number of parameters including, for example, age, sex, weight, severity of the condition being treated, the active ingredient being administered and the route of administration.

Treatment will consist of a course of 2 months we gave the patients the compositions two times daily

the first component which is tag DNA polymerase enzyme in concentration 60 u/ul in 1 ml of tranexamic acid , 20 IU one times daily.

The second injection 20 IU of monoclonal Abs ,where each injection daily contain 12 U/UI of tag DNA polymerase enzyme and 20 mg of tranexamic acid and 150 Todd of human monoclonal Abs (Antistreptolysin)

The components will be stored under sterile conditions at -20 C prior to use it is anticipated that in embodiments of the invention the compositions could not be given in combination with other forms of chemotherapy or indeed radiotherapy.

Administration :

Conjugates and compositions of and for use in the present invention may be administered to a patient in need of treatment via specific suitable route.

Some suitable routes of administration include (but are not limited to) oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural) administration. Intravenous administration is preferred.

It is envisaged that injections (subcutaneous or intramuscular) will be the primary route for therapeutic administration of compositions

Results :

The patients examined again after 2 months by ultrasonography, C.T, histopathologically, and monitoring the values of liver enzymes, AFP the results for all patients complete disappearance of liver focal lesions, ascitis with normal caliber for portal vein and disappearance of P.V thrombosis

The liver of the patients return again for their normal functions without any need for chemotherapy, radiotherapy or liver surgery.

Conclusions :

The present invention compositions have a wide clinical use for the treatment of liver cancer; it is possible that some of these components may also enter clinical use for treatment of other cancer like colon cancer, kidney cysts , heart thrombosis and liver hepatitis C. these agents are associated with no particular side effects that may help physicians for using these agents in their clinics, the incidence of significant toxicities is relatively uncommon, and no side effects such as others anti-cancer agents.

Claims

- 1-Anti-liver cancer component which is DNA polymerase as biological active enzyme.
- 2-Anti-liver cancer component which is monoclonal antibodies for streptolysin antigen.
- 3-Anti-liver cancer component which is tranexamic acid as anti-fibrinolytic agent.
- 4-The use of any one of Claim (1-2) alone or combined for treatment of liver cancer and other cancers in the body.
- 5- The use of DNA polymerase enzyme with concentration 5u/UI for treatment liver cancer and other cancers types.
- 6- The use of DNA polymerase enzyme with the previous concentration in claim (5) or others concentration for treatment liver cancer and other cancers types.
- 7- Compositions of the three components and the strategy of DNA polymerase enzyme for treatment of liver cancer and other cancers.
- 8-A method of liver cancer treatment with using DNA polymerase enzyme.
- 9-Use of DNA polymerase enzyme for treatment lesions of liver and others cancers.

AMENDED CLAIMS

received by the International Bureau on 18 November 2008

1-The using of any types of DNA polymerase in the treatment of liver cancer and other malignant lesions.

2- The using of monoclonal antibodies for streptolysin antigens in the treatment of liver cancer and other malignant lesions.

3- The using of tranexamic acid as anti fibrinolytic drug or any drug has anti fibrinolytic in the treatment of liver cancer and other malignant lesions.

4-The use of any one of Claim (1-2 and 3) alone or combined for treatment of liver cancer and other malignant lesions.

5- The use of DNA polymerase enzyme with concentration 5u/UI for treatment liver cancer and other malignant lesions. (Cancelled)

6- The use of DNA polymerase enzyme in any concentration for treatment liver cancer and other malignant lesions.

7- The using of the components in claims 1, 2 and 3 in a Composition together by any concentration for treatment of liver cancer and other malignant lesions.

8-A method of liver cancer treatment with using DNA polymerase enzyme.

9-Use of DNA polymerase enzyme for treatment lesions of liver other malignant lesions.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EG 2008/000017

A. CLASSIFICATION OF SUBJECT MATTER

IPC⁸: **A61K 38/43** (2006.01); **A61K 39/395** (2006.01); **A61K 31/195** (2006.01);
A61P 35/00 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC⁸: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, Fulltest, Medline

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Cai, J. et al. [The radiobiologic characteristics of DNA polymerase beta in hepatomas] <i>Zhonghua zhong liu za zhi</i> [Chinese journal of oncology], CHINA, 1996, Vol. 18, Nr. 1, pages 20-22 (Medline abstract NLM8732105) [online][retrieved on 17 October 2008 (17.10.2008)] <i>abstract</i>	1, 4-6, 8, 9
X	US 6475996 B1 (CAZAUX et al.) 5 November 2002 (05.11.2002) <i>abstract; column 2, lines 18-24; claim 7</i>	1, 4-6, 8, 9

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
17 October 2008 (17.10.2008)Date of mailing of the international search report
23 October 2008 (23.10.2008)Name and mailing address of the ISA/ AT
Austrian Patent Office
Dresdner Straße 87, A-1200 ViennaAuthorized officer
MOSSER R.

Facsimile No. +43 / 1 / 534 24 / 535

Telephone No. +43 / 1 / 534 24 / 437

Continuation of first sheet

Continuation No. II:

Observations where certain claims were found unsearchable

(Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: 4-9 because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 4-9 concern a method of treatment of the human or animal body by therapy (see PCT Rule 39.1(iv)) the search was carried out.

Continuation No. III:

Observations where unity of invention is lacking

(Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

There are 3 inventions:

- 1: Claims 1 and 4-9 concern DNA polymerase as anti cancer component.
- 2: Claims 2, 4 and 7 concern anti-streptolysin antibody as anti cancer component.
- 3: Claims 3 and 7 concern tranexamic acid as anti cancer component.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EG 2008/000017

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Fosså, S.D. [Cyklokapron (tranexamic acid) in the treatment of patients with advanced neoplasms] Tidsskrift for den Norske lægeforening : tidsskrift for praktisk medicin, ny række; NORWAY, 1978, Vol. 98, Nr. 28, pages 1368-1370 (Medline abstract NLM360480) [online][retrieved on 17 October 2008 (17.10.2008)] <i>title</i> ----	3

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/EG 2008/000017

Patent document cited in search report			Publication date		Patent family member(s)	Publication date
US	A	6475996			US B1 6475996	2002-11-05
					JP T 2001512962T	2001-08-28
					WO A1 9826077	1998-06-18
					EP A1 0944724	1999-09-29
					FR A1 2757178	1998-06-19