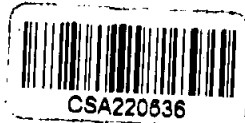
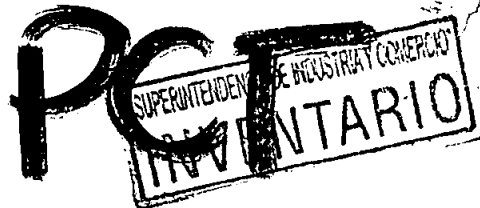


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PATENTE DE INVENCION

08-105757

EXPEDIENTE No.

Contiene los documentos relativos a la solicitud de registro de:

Título: TRATAMIENTOS PARA CÁNCER.

Clase: de la Clasificación Internacional de Niza

Solicitante : PARTHENIOS BOULIKAS.

De : ATTIKI, GRECIA.

Apoderado: MAURICIO JARAMILLO.

Bogotá, D.C., Octubre de 2008



No. 08-105757- -00006-0000

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Act. 329 CTOINFORMACION Folios: 19

de 19

SEÑOR

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: EXPEDIENTE 08 105.757.

TÍTULO SOLICITADO: TRATAMIENTO PARA EL CANCER USANDO OXALIPLATINA ENCAPSULADA EN LIPOSOMAS Y COENCAPSULAMIENTO EN LA PARTÍCULA DEL LIPOSOMA DE MAS DE UNA PREPARACIÓN FARMACÉUTICA O GENES.

PUBLICACIÓN: Gaceta 613 de 19 Febrero 2010, número de publicación 1340.

SOLICITANTE: PARTHENIOS BOULIKAS.

APODERADO: MAURICIO JARAMILLO CAMPUZANO.

TRÁMITE: SUSTENTACION DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUÍMICAS S.A.**, dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2º de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar y complementar la oposición presentada el 27 de Septiembre de 2007, en los siguientes términos:

I. RATIFICACIÓN

Comendidamente me permito insistir en los argumentos planteados en la oposición respectiva, los cuales, como se dijo en su momento, demuestran que la solicitud de la referencia incumple los requisitos de patentabilidad establecidos por los

artículos 14, 16, 18 y 20 literal d) de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario.

La solicitud colombiana en trámite incumple con los requisitos indispensables para otorgársele el privilegio de patente de invención, tal y como se demuestra con los siguientes argumentos:

- ❖ En primer lugar, y ante la reivindicación textual del uso de un liposoma para la administración de fármacos relacionados con el tratamiento del cáncer, específicamente en sus reivindicaciones 47 a 55, es relevante señalar que dicha pretensión resulta inaceptable a la luz de la Decisión 486, en tanto los “usos” son una categoría excluida del concepto de “Productos o Procedimientos” que establece el artículo 14 de la norma citada. Lo anterior, además, en consonancia con reiteradas interpretaciones de la SIC sobre este punto.
- ❖ En el mismo sentido, la solicitud colombiana en trámite incurre en otra improcedencia directa de patentabilidad al reivindicar, específicamente en sus reivindicaciones 48 y 57 a 68, un método para el tratamiento del cáncer así como una terapia de combinación para un individuo que padece dicha enfermedad, en tanto la Decisión 486 de 2000 en el artículo 20 literal d) del capítulo I del título II a cerca de las patentes de invención menciona literalmente “No serán patentables (...) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales.”
- ❖ “Las diferentes agencias sanitarias a nivel internacional han regulado fuertemente el registro de asociaciones de forma de garantizar la seguridad y eficacia de las mismas y la buena calidad en su elaboración. Todo estudio, investigación o análisis derivados de estos requisitos representan procedimientos de rutina y no originales ideas llevadas a la práctica.”¹

¹ Refiriéndonos a la ausencia de nivel inventivo de las combinaciones farmacológicas en general, es relevante mencionar el concepto de la Doctora en Bioquímica Silvia Susana Giarcovich en su opinión escrita a cerca de “Asociaciones y Patentes” en donde afirma que las asociaciones farmacológicas están restringidas por ciertos principios y lineamientos preestablecidos por varias entidades, puesto que dichas combinaciones deben estar bajo el precepto de eficacia, seguridad y eficiencia terapéutica.

- ❖ Cualquier persona medianamente versada en farmacología debe reconocer que el término “efecto sinérgico” se emplea para una forma de interacción medicamentosa que da como resultado efectos combinados o aditivos con la administración de dos o más fármacos, que resultan ser mayores que aquellos que podrían haberse alcanzado si alguno de los medicamentos se hubiera administrado solo. En otras palabras, un efecto sinérgico proveniente de una combinación de principios activos, no se puede considerar inventivo como tal, ya que se trata de un descubrimiento hecho por una persona, más no de una invención, dado que dicho efecto sinérgico o terapéutico beneficioso ocurre dentro del organismo y simplemente se reporta a través de los respectivos ensayos clínicos.

- ❖ Es importante recordar que los liposomas fueron descritos por primera vez en 1961 por Bangham A. et al. en el instituto Babraham de Cambridge. Como cualquier persona medianamente versada en la materia debe reconocer, los liposomas son estructuras vesiculares constituidas por una o más bicapas lipídicas concéntricas que encierran un número igual de compartimentos. Estas bicapas lipídicas están formadas fundamentalmente por fosfolípidos y colesterol. Dichos fosfolípidos suelen ser fosfatidilcolinas naturales o modificadas (dimiristoil, dipalmitoil o diesteroilfosfatidilcolinas). A estos fosfolípidos se le pueden adicionar otros, bien sean aniónicos o catiónicos, que confieren a los liposomas una carga neta superficial positiva o negativa. Es evidente que estas son absolutamente todas las características de los liposomas descritos en la solicitud colombiana, lo que resalta que se tratan de liposomas convencionales.

- ❖ En el estado de la técnica, también se reconoce con anterioridad la utilidad de dichos liposomas para la inclusión de diversos agentes anticancerígenos, lo que pone en evidencia de nuevo la carencia de nivel inventivo en la aplicación de dichas formulaciones. Algunos documentos que pueden soportar lo anteriormente dicho son, por ejemplo, la patente americana US3993754: “Liposome-encapsulated actinomycin for cancer chemotherapy” publicada el 23 de noviembre de 1973, la publicación internacional WO9325225A1: LIPOSOMAL FORMULATIONS FOR ADMINISTERING TO CANCER PATIENTS publicada el 23 de diciembre de 1993 y la patente americana

US6096336: "Liposomal prodrugs comprising derivatives of camptothecin and methods of treating cancer using these prodrugs" publicada el 01 de Agosto de 2000.

- ❖ La publicación internacional WO/2001/34130 publicada el 17 de mayo de 2001 y titulada "THERAPY FOR HUMAN CANCERS USING CISPLATIN AND OTHER DRUGS OR GENES ENCAPSULATED INTO LIPOSOMES." revela todo lo relacionado a la formación de liposomas que pueden contener agentes anticancerígenos solos o en combinación con otros fármacos o genes útiles en el tratamiento de cáncer, en donde se describe detalladamente el proceso de obtención de dichos liposomas, a través de la asociación de lípidos cargados negativamente y la inclusión de fármacos con carga preferencialmente positiva para dar origen a una micela inicial. Coincide también con la solicitud colombiana en cuestión, la proporción entre dichos lípidos y dichos fármacos, así como el mismo tipo de lípidos y el mismo tipos de solvente (etanol) bajo el cual se lleva a cabo dicha elaboración de los liposomas. De la misma manera se hace mención de la inclusión o conjugación con un polímero tal como el PEG y compuestos de carácter peptídico, en donde dichos compuestos peptídicos coinciden en la función de asignar especificidad a la formulación al ser un ligando específico. Si bien es cierto que esta anterioridad esta enfocada a la formulación del compuesto cisplatino, es importante resaltar que la anterioridad da la información suficiente para que cualquier persona medianamente versada en la materia que requiera formular oxaliplatino en este mismo tipo de liposomas, pueda hacerlo, guiándose a través de los principios aquí divulgados.
- ❖ La patente americana US 2004/022842 publicada el 05 de febrero de 2004 y titulada "LIPOSOME PREPARATIONS CONTAINING OXALIPLATIN" revela con detalle la formación de liposomas que contienen oxaliplatino y que a su vez se asocian tanto con un polímero como con un ligando, tal y como sucede en el caso de los liposomas reivindicados por la solicitud colombiana en tramite. Si bien es cierto que en esta anterioridad se da prevalencia a la transferrina como ligando, igualmente es cierto que se da la suficiente información como para guiar a cualquier persona medianamente versada en la materia que quiera involucrar otros tipos de ligandos dentro de los liposomas descritos.

- ❖ La publicación internacional WO/2001/93836 publicada el 13 de diciembre de 2001 y titulada “ENCAPSULATION OF PLASMID DNA (LIPOGENES) AN THERAPEUTIC AGENTS WITH NUCLEAR LOCALIZATION SIGNAL/FUSOGENIC PEPTIDE CONJUGATES INTO TARGETED LIPOSOME COMPLEXES” revela con detalle la inclusión de material genético (secuencias de ADN) en liposomas en donde además también se pueden incluir fármacos anticancerígenos, así como la conjugación con ligandos que buscan darle mayor especificidad a la formulación. Específicamente coincide con la solicitud colombiana en trámite, en la inclusión de oxaliplatino así como los mismos tipos de lípidos que componen el liposoma (DMRIE, DMTAP, DOGS, DOTAP, DOTMA, DPTAP y DSTAP.)
- ❖ Se concluye que todos los elementos que sustentan la invención de la solicitud colombiana en cuestión, consisten en una simple agregación de elementos reconocidos en el estado de la técnica, tales como la combinación farmacológica entre compuestos anticancerígenos y material genético; las técnicas y el conocimiento para lograr la inclusión de dichas combinaciones dentro de un liposoma convencional y las técnicas y conocimientos para adicionar ligandos que permitan una mayor especificidad de la formulación en el tratamiento de ciertos tipos de cáncer.

II. COMPLEMENTO DE INFORMACIÓN

Refiriéndonos nuevamente a la carencia de nivel inventivo de la solicitud colombiana en trámite, podemos citar nuevos documentos que evidencian que información de diverso tipo, podría servir de guía para una persona medianamente versada en la elaboración de productos farmacéuticos que requiriera formular fármacos anticancerígenos en formulaciones liposomales con las mismas características que las que posee lo reivindicado por la solicitud Colombiana en trámite.

En primer lugar la publicación internacional WO 2004/054499 publicada el 01 de Julio de 2004 coincide con el rango de proporción entre el material lipídico y el compuesto anticancerígeno que va a ser incluido en el liposoma. Mas específicamente, menciona cisplatino, que corresponde a uno de los mismos agentes anticancerígenos reivindicados en la solicitud colombiana en cuestión, veamos:

- 1) A composition comprising a liposome or lipid complex and an entrapped active platinum compound, the liposome or lipid complex containing one or more lipids, wherein the active platinum compound to lipid ratio is from 1:50 to 1:2 by weight.

(...)

- 4) The composition of claim 1, wherein the active platinum compound is cisplatin.

De la misma manera las publicaciones científicas "Gemcitabine Combined With Cisplatin As First-Line Treatment In Patients 60 Years Or Older With Epithelial Ovarian Cancer: A Phase II Study" y "Gemcitabine And Cisplatin In The Treatment Of Advanced Or Metastatic Pancreatic Cancer" revelan con anterioridad la eficacia de la combinación farmacológica entre gemcitabina y cisplatina, lo que afectaría la novedad en cuanto al uso dicha asociación para tratar cáncer, veamos:

Gemcitabine Combined With Cisplatin As First-Line Treatment In Patients 60 Years Or Older With Epithelial Ovarian Cancer: A Phase II Study².

Abstract: *This phase II study evaluated the activity and toxicity of gemcitabine plus cisplatin as first-line treatment of patients with advanced ovarian cancer. Chemonaive patients ≥ 60 -year-old with FIGO stage IIIC or IV epithelial ovarian carcinoma were enrolled. Patients received cisplatin 75 mg /m² on day 1 and gemcitabine 1250 mg /m² on day 1 (before cisplatin) and day 8 of a 21-day cycle. Of 44 female patients (median age, 70 years), 72.7% had stage IIIC disease and 67.4% had a Karnofsky performance status ≥ 80 . Of the 37 response-evaluable patients (35 with measurable lesion[s] ≥ 2 cm), there were seven (18.9%) pathologic complete responses, two (5.4%) pathologic partial responses, two (5.4%) clinical complete responses, and 12 (32.4%) clinical partial responses, for an overall response rate of 62.2% (95% CI, 44.8%-77.5%), and a pathologic response rate of 24.3% (95% CI, 11.8%-41.2%). Median survival was 27.7 months (95% CI, 14.3-40.8 months). Grade 3/4 neutropenia and thrombocytopenia occurred in 59.5% and 30.2% of patients, respectively, with neutropenic fever in*

² Bauknecht T, Hefti A, Morack G, Villena-Heinsen C, Wallwiener D, Elling D, Minckwitz GV, Mansouri K, Blatter J, Breitbach GP. Int J Gynecol Cancer. 2003 Mar-Apr;13(2):130-7.

one patient. Grade 3 nausea /vomiting and alopecia occurred in 25.6% and 9.5% of patients, respectively. We conclude that gemcitabine plus cisplatin is active and feasible as first-line treatment of advanced epithelial ovarian cancer in patients ≥ 60 years. Further clinical trials adding gemcitabine to current standard, first-line treatment seem warranted in younger as well as older patients.

Gemcitabine And Cisplatin In The Treatment Of Advanced Or Metastatic Pancreatic Cancer³.

Abstract: *BACKGROUND: This phase II study was initiated to determine the efficacy and safety of gemcitabine plus cisplatin in patients with pancreatic cancer.*

PATIENTS AND METHODS: Gemcitabine 1000 mg/m² was given on days 1, 8, and 15 of a 28-day schedule, and cisplatin 50 mg/m² on days 1 and 15 to chemonaive patients with locally advanced or metastatic pancreatic cancer.

RESULTS: Of the 41 patients enrolled (median age 57, and 61% male), median Karnofsky performance status was 80%. Patients received a median of 4.2 cycles (range 1-11). In 35 evaluable patients, one complete response (CR) and three partial responses (PR) were observed, for an overall response rate of 11% (95% confidence interval (95% CI): 3.2% -26.7%). Stable disease (SD) > 3 months occurred in 20 (57%) patients; 6 survived ≥ 1 year. Median time to progressive disease was 4.3 months (95% CI: 3.0-5.7 months). For all patients, median survival was 8.2 months (95% CI: 6.1-10.6 months) with a one-year survival rate of 27%. Therapy was well tolerated. Grade 3-4 neutropenia (no grade 3-4 infection), thrombocytopenia (no bleeding), nausea/vomiting, and alopecia were reported in 29%, 13%, and 2.6% of patients, respectively.

CONCLUSIONS: The combination of gemcitabine and cisplatin is a moderately active treatment for patients with locally advanced and metastatic pancreatic cancer without compromising tolerability.

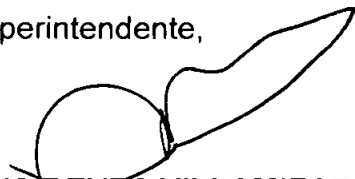
Con lo anterior, y junto a la información expuesta en su momento en la oposición, queda claro que tanto la combinación de los fármacos que reivindica la solicitud colombiana en cuestión, como la inclusión de los mismos en formas farmacéuticas tales como los liposomas, son dos estrategias técnicas y terapéuticas lo suficientemente descritas y utilizadas como para poder sustentar una invención, y por el contrario, a partir de dicha información anterior, fácilmente puede derivarse el contenido de la solicitud colombiana en trámite.

Por todo lo anterior, ruego se analicen los argumentos expuestos con el rigor y detenimiento habituales y que en consecuencia se decrete, además de la negación de la solicitud en comento, el archivo del expediente que la contiene.

III. ANEXOS.

- ❖ Copia de las publicaciones científicas "Gemcitabine Combined With Cisplatin As First-Line Treatment In Patients 60 Years Or Older With Epithelial Ovarian Cancer: A Phase II Study" y "Gemcitabine And Cisplatin In The Treatment Of Advanced Or Metastatic Pancreatic Cancer".
- ❖ Capitulo reivindicatorio de la publicación internacional WO 2004/054499 publicada el 01 de Julio de 2004.

Señor Superintendente,



JOSE LUIS REYES VILLAMIZAR
C.C. 79.152.473 de Usaquén
T.P. 44655 del C. S de la J.

³ Heinemann V, Wilke H, Mergenthaler HG, Clemens M, König H, Illiger HJ, Arning M, Schalhorn A, Possinger K, Fink U. Ann Oncol. 2000 Nov;11(11):1399-403.

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- (71) Applicant: **TRANSAGE, INC.** [—/US]; 7 Deer Park Drive, Suite N, Monmouth Junction, NJ 08852 (US).
- (72) Inventors: **LEE, Jin**; 46 McElroy Lane, Belle Mead, NJ 08502 (US). **MILLER, Brian, S.**; 20 Guilford Lane, Mercerville, NJ 08619 (US). **WU, Fangjun**; 74 E. McClellan Avenue, Livingston, NJ 07039 (US). **BONI, Lawrence, T.**; 40 Cummings Road, Monmouth Junction, NJ 08852 (US).
- (74) Agent: **JACKSON, Arthur, E.**; Dechert LLP, P.O. Box 5218, Princeton, NJ 08543 (US).
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- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*



WO 2004/054499 A2

(54) Title: PLATINUM AGGREGATES AND PROCESS FOR PRODUCING THE SAME

(57) Abstract: A composition and process for making the composition, the composition comprising a liposome and active platinum compound, the liposome containing one or more lipids, with a high active platinum compound to lipid ratio.

Claims:

- 1) A composition comprising a liposome or lipid complex and an entrapped active platinum compound, the liposome or lipid complex containing one or more lipids, wherein the active platinum compound to lipid ratio is from 1:50 to 1:2 by weight.
- 2) The composition of claim 1, wherein the active platinum compound to lipid ratio is from 1:50 to 1:5 by weight.
- 3) The composition of claim 1, wherein the active platinum compound to lipid ratio is from 1:50 to 1:10 by weight.
- 4) The composition of claim 1, wherein the active platinum compound is cisplatin.
- 5) The composition of claim 1, wherein the active platinum compound to lipid ratio is from 1:25 to 1:15 by weight.
- 6) The composition of claim 5, wherein the active platinum compound is cisplatin.
- 7) The composition of claim 6, the one or more lipids comprise DPPC.
- 8) The composition of claim 7, the one or more lipids comprise cholesterol.
- 9) The composition of claim 7, the one or more lipids comprise 50-100 [90?] mol% DPPC and 0-50 mol% cholesterol.
- 10) The composition of claim 7, the one or more lipids comprise 50-65 mol% DPPC and 35-50 mol% cholesterol.
- 11) A process for making a platinum aggregate comprising the steps of:

- (a) combining an active platinum compound and a hydrophobic matrix carrying system;
- (b) establishing the mixture at a first temperature; and
- (c) thereafter establishing the mixture at a second temperature, which second temperature is cooler than the first temperature;

wherein the steps (b) and (c) are effective to increase the encapsulation of active platinum compound.

- 12) The process of claim 11, further comprising sequentially repeating the steps (b) and (c) for a total of two or more cycles.
- 13) The process of claim 11, wherein the active platinum compound solution is produced by dissolving active platinum compound in a saline solution to form a platinum solution.
- 14) The process of claim 13, wherein the active platinum compound is cisplatin
- 15) The process of claim 11, wherein the hydrophobic matrix carrying system comprises liposome or lipid complex-forming lipids.
- 16) The process of claim 15, wherein the one or more lipids comprise DPPC.
- 17) The process of claim 15, wherein the one or more lipids further comprise cholesterol.
- 18) The process of claim 11, wherein the hydrophobic matrix carrying system is produced by dissolving one or more lipids in ethanol to form a lipid solution and injecting the lipid solution into an aqueous medium containing active platinum compound.
- 19) The process of claim 11, further comprising sequentially repeating the steps (b) and (c) for a total of three or more cycles.
- 20) The process of claim 19, wherein the step (c) comprises establishing the mixture at a temperature from -25 degrees Celsius to 25 degrees Celsius.

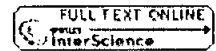
- 21) The process of claim 19, wherein step (c) comprises establishing the mixture at a temperature from -5 degree Celsius to 5 degrees Celsius.
- 22) The process of claim 19, wherein the step (b) comprises establishing the mixture at a temperature from 4 degrees Celsius to 75 degrees Celsius.
- 23) The process of claim 19, wherein the step (b) comprises establishing the mixture at a temperature from 45 degrees Celsius to 55 degrees Celsius.
- 24) The process of claim 11, wherein the temperature differential between steps (b) and (c) is 25 degrees Celsius or more.
- 25) The process of claim 24, wherein the temperature established in step (b) is 50 degrees Celsius or more.
- 26) The process of claim 11, wherein the temperature established in step (b) is 50 degrees Celsius or more.
- 27) A platinum aggregate produced by the method of claim 11.
- 28) A platinum aggregate produced by the method of claim 14.
- 29) A pharmaceutical formulation comprising the composition of claim 1 and a pharmaceutically acceptable carrier or diluent.
- 30) A pharmaceutical formulation comprising the composition of claim 1, adapted for inhalation by a patient.
- 31) A pharmaceutical formulation comprising the composition of claim 1, adapted for injection into a patient.

32) The process of claim 11, further comprising, after all of steps (b) and steps (c) have been completed:

- (d) removing un-entrapped active platinum compound by filtering through a membrane having a molecular weight cut-off selected to retain desired liposomes or lipid complexes and adding a liposome or lipid complex compatible liquid to wash out un-entrapped active platinum compound.

PubMed

U.S. National Library of Medicine
National Institutes of Health



Display Settings: Abstract

[Int J Gynecol Cancer](#). 2003 Mar-Apr;13(2):130-7.

Gemcitabine combined with cisplatin as first-line treatment in patients 60 years or older with epithelial ovarian cancer: a phase II study.

Bauknecht T, Hefti A, Morack G, Villena-Heinsen C, Wallwiener D, Elling D, Minckwitz GV, Mansouri K, Blatter J, Breitbach GP.

Eli Lilly GmbH Deutschland, Bad Homburg v.d.H. Germany. Bauknecht_Thomas@Lilly.com

Comment in:

[Int J Gynecol Cancer](#). 2005 Jan-Feb;15(1):180-1.

Abstract

This phase II study evaluated the activity and toxicity of gemcitabine plus cisplatin as first-line treatment of patients with advanced ovarian cancer. Chemonaive patients ≥ 60 -year-old with FIGO stage IIIC or IV epithelial ovarian carcinoma were enrolled. Patients received cisplatin 75 mg /m² on day 1 and gemcitabine 1250 mg /m² on day 1 (before cisplatin) and day 8 of a 21-day cycle. Of 44 female patients (median age, 70 years), 72.7% had stage IIIC disease and 67.4% had a Karnofsky performance status ≥ 80 . Of the 37 response-evaluable patients (35 with measurable lesion[s] ≥ 2 cm), there were seven (18.9%) pathologic complete responses, two (5.4%) pathologic partial responses, two (5.4%) clinical complete responses, and 12 (32.4%) clinical partial responses, for an overall response rate of 62.2% (95% CI, 44.8%-77.5%), and a pathologic response rate of 24.3% (95% CI, 11.8%-41.2%). Median survival was 27.7 months (95% CI, 14.3-40.8 months). Grade 3/4 neutropenia and thrombocytopenia occurred in 59.5% and 30.2% of patients, respectively, with neutropenic fever in one patient. Grade 3 nausea /vomiting and alopecia occurred in 25.6% and 9.5% of patients, respectively. We conclude that gemcitabine plus cisplatin is active and feasible as first-line treatment of advanced epithelial ovarian cancer in patients ≥ 60 years. Further clinical trials adding gemcitabine to current standard, first-line treatment seem warranted in younger as well as older patients.

PMID: 12657112 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, Substances

LinkOut - more resources

Gemcitabine and cisplatin in the treatment of advanced or metastatic pancreatic cancer

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Klinikum Grosshadern, München; ²Westdeutsches Tumorzentrum, Essen; ³Medizinische Klinik II der Charité, Berlin; ⁴Medizinische Klinik der Universität Tübingen, Tübingen; ⁵Medizinische Universitätsklinik Erlangen, Erlangen; ⁶Städt. Klinik, Abteilung Hämatologie Onkologie, Oldenburg; ⁷Lilly Deutschland GmbH, Bad Homburg; ⁸Klinikum Rechts der Isar, München, Germany

Summary

Background: This phase II study was initiated to determine the efficacy and safety of gemcitabine plus cisplatin in patients with pancreatic cancer.

Patients and methods: Gemcitabine 1000 mg/m² was given on days 1, 8, and 15 of a 28-day schedule, and cisplatin 50 mg/m² on days 1 and 15 to chemo-naïve patients with locally advanced or metastatic pancreatic cancer.

Results: Of the 41 patients enrolled (median age 57, and 51% male), median Karnofsky performance status was 80%. Patients received a median of 4.2 cycles (range 1–11). In 35 evaluable patients, one complete response (CR) and three partial responses (PR) were observed, for an overall response rate of 11% (95% confidence interval [95% CI]: 3.2%–26.7%).

Stable disease (SD) > 3 months occurred in 20 (57%) patients; 6 survived ≥ 1 year. Median time to progressive disease was 4.3 months (95% CI: 3.0–5.7 months). For all patients, median survival was 8.2 months (95% CI: 6.1–10.6 months) with a one-year survival rate of 27%. Therapy was well tolerated. Grade 3–4 neutropenia (no grade 3–4 infection), thrombocytopenia (no bleeding), nausea/vomiting, and alopecia were reported in 29%, 13%, and 2.6% of patients, respectively.

Conclusions: The combination of gemcitabine and cisplatin is a moderately active treatment for patients with locally advanced and metastatic pancreatic cancer without compromising tolerability.

Key words: cisplatin, combination chemotherapy, gemcitabine, pancreatic cancer, prolonged survival

Introduction

Pancreatic cancer is currently the fifth leading cause of cancer mortality [1]. While surgery is the only curative treatment, most tumors (85%–90%) are not resectable at the time of diagnosis. In untreated unresectable disease, a median survival of three to six months is observed. So far, the role of chemotherapy has been limited to disease palliation. The activity of chemotherapy in pancreatic cancer is generally considered to be modest, and most phase-II-clinical trials evaluating new agents have failed to identify single agents with an objective response rate consistently above 10% [2]. Moreover, survival has not been improved by chemotherapy compared with best supportive care. Of all cytostatics tested, intravenous 5-fluorouracil (5-FU) has most commonly been used, both alone and in combination with other agents.

In a randomized study, Burris et al. [3] demonstrated that gemcitabine was superior to 5-FU with regard to both survival and improvement of disease-related symptoms [4]. While the median survival achieved by gemcitabine was less than six months in this study, 18% of patients survived longer than one year compared to a one-year survival of only 2% in patients treated with 5-FU alone [3]. Furthermore, preclinical studies have

shown that gemcitabine and cisplatin, which have demonstrated activity in pancreatic cancer [5–8] interact synergistically [9]. Therefore, a phase II study was initiated to determine the impact of a gemcitabine plus cisplatin combination treatment on efficacy, toxicity, and quality of life in patients with advanced pancreatic cancer.

Patients and methods

Patient selection

Patients with histologically or cytologically confirmed locally advanced (stage III, T₁₋₄, N₁) or metastatic (stage IV, T₁₋₄, N₀₋₁, M₁) pancreatic cancer were enrolled into this study. Tumor lesions were required to be bidimensionally measurable at a minimum size of 1 cm × 1 cm. Patients who had received prior chemo- or radiotherapy were not included. Other eligibility criteria were age ≥ 18 years, life expectancy ≥ 12 weeks, Karnofsky performance status ≥ 60%, and adequate bone marrow reserve (white blood cell count ≥ 3.5 × 10⁹/l, platelets ≥ 100 × 10⁹/l, and hemoglobin ≥ 100 g/l). Patients with ampullary, peri-ampullary, bile duct cancers, endocrine tumors of the pancreas or lymphoma of the pancreas were excluded from this study. Central nervous system (CNS) metastases and second primary malignancies were also criteria for exclusion, as were inadequate liver function (bilirubin ≥ 1.5 mg/dl, abnormal prothrombin time, and alanine trans-

aminase (ALT) and aspartate transaminase (AST) levels greater than three times the normal levels in patients with no liver metastases, whereas AST and ALT levels could be up to five times the normal values in patients with known liver metastases), pregnancy or breast feeding, active infection, and serious concomitant disorders. This study was conducted according to the ethical principles stated in the Declaration of Helsinki, and was approved by the Ethics Committee of our Institute. Written informed consent was obtained from all patients before entering the study.

Study design

In this multicenter, non-randomized study, patients were treated with a combination of gemcitabine 1000 mg/m² (as a 30-minute i.v. infusion) on days 1, 8 and 15 and cisplatin 50 mg/m² (as a one-hour i.v. infusion before gemcitabine administration) on days 1 and 15 of a 28-day cycle. Patients were adequately prehydrated prior to cisplatin administration. Doses were modified based on weekly blood counts in order to maintain a tolerable toxicity profile. Doses of gemcitabine and cisplatin were reduced to 50% when the absolute granulocyte count dropped to $0.5-0.99 \times 10^9/l$ or when the platelet count decreased to $50-74 \times 10^9/l$. Doses were withheld when granulocyte or platelet counts were $<0.5 \times 10^9/l$ or $<50 \times 10^9/l$, respectively. Patients who sustained febrile neutropenia, World Health Organization (WHO) grade 4 thrombocytopenia, or bleeding associated with thrombocytopenia received a 50% dose reduction. Doses could subsequently be increased if the 50% dose level was well tolerated. Prophylactic antiemetics were permitted, as were growth factors, if required.

Baseline and treatment assessments

Before treatment, the disease state of each patient was evaluated by full medical history, analgesic requirements, performance status, and disease-related symptoms via quality of life (QoL) measurements. They also received chest X-ray, as well as measurement of visible or palpable lesions, and were asked to complete a cancer-specific QoL questionnaire, the EORTC QLQ-C30 [10]. Other pre-treatment evaluations included a full blood count, differential blood count, and prothrombin time measurements. Blood chemistries were also measured, along with urine analysis, electrocardiogram (ECG), and vital signs.

Efficacy was assessed during treatment with limited physical examination, weight measurement, analgesic use, performance status, QoL questionnaire, and disease-related symptoms before each treatment cycle. Additionally, chest X-ray and radiological imaging were performed every other treatment cycle to demonstrate disease status. Tumor measurement was assessed using computerized tomography (CT) or magnetic resonance imaging (MRI). Patients who received at least three doses of gemcitabine and two doses of cisplatin and who had bidimensionally measurable, cytologically or histologically confirmed disease were evaluable for efficacy. Patients who discontinued treatment due to toxicity prior to receiving three doses of gemcitabine and two doses of cisplatin were also considered evaluable for efficacy.

Patients who received at least one dose of gemcitabine and cisplatin were considered evaluable for safety. A full blood count was taken on each day of treatment, and blood chemistry at the start of each cycle. Toxicity was evaluated throughout the study. Patients were discontinued from the study when the treatment was associated with unacceptable toxicities or lack of efficacy, or at the patient's or investigator's request.

Tumor assessments and toxicity were evaluated using standard WHO criteria. A complete tumor response was defined as disappearance of all clinical evidence of tumor for a minimum of four weeks. Partial response was defined as $\geq 50\%$ decrease in the sum of the products of two perpendicular diameters of measurable lesions for a minimum of four weeks. During this time, there must have been no increase of $\geq 25\%$ in the size of any single lesion or the appearance of any new lesion. Stable disease was defined as a decrease of total tumor size $< 50\%$ or an increase $< 25\%$. Progressive disease was defined as an increase in the sum of the products of the diameters of measurable lesions by $\geq 25\%$ or the appearance of any new lesion.

Table 1. Baseline characteristics.

	All patients	Evaluable patients
Number of patients	41	35
Age (years)		
Median	57	58
Range	33-74	33-74
Sex		
Male	25	20
Female	16	15
Performance status (median = 80), n (%)		
100	7 (17.1)	6 (17.1)
90	11 (26.8)	10 (28.6)
80	11 (26.8)	10 (28.6)
70	11 (26.8)	8 (22.9)
60	1 (2.4)	1 (2.9)
Disease stage, n (%)		
IIIb	6 (14.6)	6 (17.1)
IV	35 (85.4)	29 (82.9)
Number of metastatic disease sites, n (%)		
1	18 (43.9)	15 (42.9)
2	16 (39.0)	13 (37.1)
3	6 (14.6)	6 (17.1)
4	1 (2.4)	1 (2.9)

Results

Between August 1994 and May 1996, 41 chemo-naïve patients were enrolled in the study from 7 centers. The median follow-up was 8.2 months. The median age of patients was 57 (range 33-74) years, and 25 patients were male. Patient characteristics at entry are summarized in Table 1. The majority of patients (85%) had metastatic disease, with liver metastases in 71%, lymph node involvement in 15%, and lung metastases in 7% of patients. Patients presenting with only one measurable site of disease suffered from liver metastasis; however, the primary tumor had been operated on or was not measurable in its extent. Only six patients categorized with stage IIIb disease were evaluated exclusively on the basis of their primary pancreatic lesions. Thirty-five patients had prior surgery, twenty-six of these for diagnostic purposes, nine for palliation. Four patients did not receive sufficient therapy to be evaluable for efficacy, one had an unconfirmed diagnosis, and one had received prior chemotherapy. All patients were evaluable for toxicity.

Tumor response

Response to treatment with gemcitabine and cisplatin is summarized in Table 2. Of the 35 patients evaluable for response, 1 complete response (CR) and 3 partial responses (PR) were observed, for an overall response rate of 11% (95% confidence interval (95% CI): 3.2%-26.7%). One additional patient achieved CR but the response was not confirmed after one month. The patient achieving a complete response and two patients with partial response presented with liver metastases. In addition, 20 (57%) evaluable patients reported a best

Table 2. Tumor response (n = 35).

Tumor response	n (%)
Complete response (CR)	1 (2.9)
Partial response (PR)	3 (8.6)
Stable disease (SD)	20 (57.1)
Progressive disease (PD)	10 (28.6)
Not done ^a	1 (2.9)
Total responders (CR + PR)	4 (11.4)

^a One patient achieved a complete response; however, response confirmation after one month was not performed.

Table 3. Mean EORTC QLQ-C30 scores (standard deviation).

	All patients (n = 31)		Responders (n = 4)	
	Baseline	Endpoint	Baseline	Endpoint
Functional scales (0–100; 100 = perfect functioning)				
Physical	76.0 (25.5)	65.2 (30.5)	95.0 (10.0)	85.0 (30.0)
Role	61.3 (33.4)	45.2 (39.5) ^a	87.5 (25.0)	75.0 (28.9)
Cognitive	83.3 (23.6)	82.8 (21.3)	87.5 (25.0)	87.5 (16.0)
Emotional	53.5 (27.1)	64.4 (25.5)	37.5 (19.8)	70.8 (25.9)
Social	53.8 (29.7)	47.8 (35.4)	54.2 (28.5)	58.3 (31.9)
Global QoL	51.1 (19.5)	50.8 (22.6)	62.5 (16.0)	70.8 (25.0)
Symptom scales (0–100; 0 = no symptoms)				
Fatigue	51.9 (28.0)	53.1 (31.3)	55.6 (33.3)	18.5 (17.0)
Nausea/vomiting	12.9 (21.8)	22.0 (30.8) ^a	4.2 (8.3)	12.5 (16.0)
Pain	42.5 (32.4)	26.9 (27.1) ^a	33.3 (38.5)	4.2 (8.3)
Dyspnea	8.9 (21.3)	20.0 (25.7)	22.2 (38.5)	0.0 (0.0)
Insomnia	46.7 (32.3)	24.4 (28.9) ^a	44.4 (19.2)	11.1 (19.2)
Appetite loss	44.4 (39.5)	44.4 (37.5)	44.4 (38.5)	33.3 (33.3)

^a P < 0.05.

response of stable disease lasting ≥ 3 months. Median time to progressive disease was 4.3 months (95% CI: 3.0–5.7 months). Based on an intent-to-treat analysis for all 41 patients, the median survival time was 8.2 months (95% CI: 6.1–10.6 months), and the one-year survival rate was 27%. The survival curve is shown in Figure 1. For evaluable patients the median survival time was 8.3 months (range 0.5–26+ months). The one-year survival rate for 35 evaluable patients was 28%, while 69% were alive at 6 months and 43% were alive at 9 months. The patient who reported a complete response was still alive 26 months after study entry, while those patients with partial responses survived to 8.5, 12, and 21 months, respectively. Extended survival was also seen in a number of patients whose best response was stable disease. Six (30%) patients with stable disease survived for at least twelve months from study entry, and three patients had survival times of fifteen, twenty-one, and twenty-four months, respectively.

Other measures of efficacy

Analgesia levels were also monitored in order to assess efficacy in this patient cohort. Of the 19 patients who had a baseline analgesia score of 1, 2, or 3, nine showed

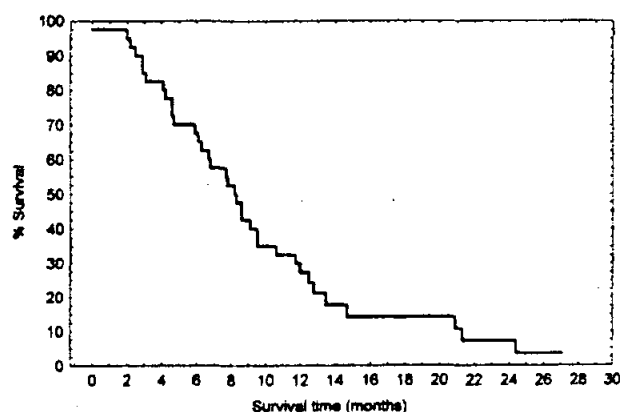


Figure 1. Kaplan-Meier survival curve for all patients treated with gemcitabine and cisplatin.

an improvement, requiring a reduced level of analgesic. Three of the eleven patients who had a baseline score of 3 (oral morphine, methadone) reported a decreased need for analgesia use to a minimum level of 0 (needing no analgesia). These improvements lasted for 70–250 days during the time of study follow-up. These patients usually discontinued analgesia consumption by the second infusion of gemcitabine. Performance status improved for 15 patients, including 6 of 8 patients who had a baseline score of 70. The performance score of one of these patients improved to 100, while another improved to 90.

Thirty-eight (93%) patients completed at least one QoL questionnaire (median 3.5, range 1–10). Thirty-one patients who completed a baseline and at least one post-baseline questionnaire were included in the analysis. Mean scores of functional scales and select symptom scales are reported in Table 3.

Overall, patients noted a worsening of their physical, role, and social functioning, but the change was only statistically significant ($P < 0.05$) for role functioning. Emotional functioning was slightly improved, while cognitive and global quality of life were essentially unchanged. Patients noted statistically significant ($P < 0.05$) improvement in pain and insomnia. Nausea/vomiting and dyspnea worsened, but the change was statistically significant ($P < 0.05$) only for nausea and vomiting. Responders noted marked improvement in emotional functioning, fatigue, pain, dyspnea (mean score of 0), and insomnia, but these changes were not statistically significant perhaps due to the small number of patients in this subgroup.

Laboratory toxicity

As demonstrated in Table 4, renal and hepatic toxicity remained low during combination treatment with gemcitabine and cisplatin, with WHO grade 3–4 toxicities reported in less than 6% of patients. Hematological toxicity was moderate. Grades 3 and 4 neutropenia were observed in 10 (29%) and 2 (6%) patients, leukopenia in 2 (5%) and 0 patients, anemia in 5 (13%) and 0

Table 4. Laboratory toxicity – maximum WHO grades ($n = 41$).

Toxicity parameter	Number of patients with data	Maximum calculated WHO grades				
		0 (%)	1 (%)	2 (%)	3 (%)	4 (%)
Alkaline phosphatase	35	45.7	34.3	14.3	2.9	2.9
Alanine transaminase (ALT)	35	80.0	8.6	5.7	5.7	0.0
Aspartate transaminase (AST)	35	80.0	14.3	2.9	0.0	2.9
Bilirubin	35	85.7	5.7	2.9	5.7	0.0
Blood urea nitrogen	35	94.3	5.7	0.0	0.0	0.0
Creatinine	35	97.1	0.0	0.0	2.9	0.0
Hemoglobin	39	15.4	33.3	38.5	12.8	0.0
White blood cells	39	25.6	28.2	41.0	5.1	0.0
Segmented neutrophils*	35	31.4	14.3	20.0	28.6	5.7
Platelets	38	31.6	7.9	31.6	15.8	13.2

* Segmented neutrophils were converted to WHO scores using granulocyte count criteria.

Table 5. Non-laboratory toxicity, maximum WHO grades ($n = 41$).

Toxicity parameter	Number of patients with data	Maximum WHO grades				
		0 (%)	1 (%)	2 (%)	3 (%)	4 (%)
Constipation	39	79.5	15.4	0.0	5.1	0.0
Cutaneous	39	89.7	5.1	5.1	0.0	0.0
Diarrhea	39	79.5	12.8	5.1	2.6	0.0
Fever	39	84.6	7.7	7.7	0.0	0.0
Hair	39	53.8	30.8	12.8	2.6	0.0
Hemorrhage	39	87.2	10.3	2.6	0.0	0.0
Infection	39	87.2	5.1	7.7	0.0	0.0
Nausea/vomiting	39	20.5	33.3	33.3	10.3	2.6
Oral	39	79.5	20.5	0.0	0.0	0.0
Pain	39	92.3	0.0	7.7	0.0	0.0
Peripheral neurotoxicity	39	87.2	5.1	7.7	0.0	0.0
Pulmonary	39	97.4	2.6	0.0	0.0	0.0
Cardiac rhythm	39	89.7	10.3	0.0	0.0	0.0
State of consciousness	39	89.7	5.1	2.6	0.0	2.6

patients, and thrombocytopenia in 6 (16%) and 5 (13%) patients, respectively. The clinical impact of these toxicities, however, was negligible: there was no grade 3 or 4 infection, and no bleeding episodes were reported.

Non-laboratory toxicity

As shown in Table 5, non-laboratory toxicities with gemcitabine and cisplatin were infrequent. The most frequently reported event was nausea/vomiting, with WHO grade 3 toxicity observed in four (10%) patients, and grade 4 in one (3%) patient. One (3%) patient had grade 3 diarrhea, and two (5%) had grade 3 constipation. Hair loss was uncommon with more than half the patients reporting no hair loss, and only one (3%) patient with grade > 2 alopecia (grade 3). Flu-like symptoms, which have been reported in other gemcitabine studies, were not seen in this trial.

Dose omissions and reductions

Of the 515 planned doses of gemcitabine, 103 (20%) were reduced and 56 (11%) were omitted. Thrombocytopenia was the main cause of dose reduction (63%), followed by leukopenia (15%). Thrombocytopenia was responsible for 52% of gemcitabine dose omissions. Of the 344 planned cisplatin infusions, 78 (23%) were reduced and 47 (14%) were omitted. Leukopenia was responsible for 17% of dose reductions and thrombocytopenia for 65%, while thrombocytopenia and leukopenia caused 47% and 9% of dose omissions, respectively.

Discussion

The results of this study indicate that the combination of gemcitabine and cisplatin is an attractive treatment option for patients with locally advanced or metastatic pancreatic cancer. While the overall response rate (CR + PR) of 11% was considered modest, stable disease (SD) was achieved in an additional 57% of patients. In other words, primary progression of the disease could be arrested, at least transiently, in 69% of patients. Including SD with CR and PR rates may better reflect the true benefit of chemotherapy than the classical response rate defined by CR + PR. This is especially true in pancreatic cancer, in which conventional imaging procedures show classical tumor response only late during the course of effective therapy [2, 11]. In this study, PR + CR were observed in four patients after treatment with 4, 6, 10, and 10 cycles, respectively. The importance of stable disease as a reasonable treatment goal is further emphasized by the observation that 30% of patients with SD in this study survived longer than one year.

The positive impact of the gemcitabine plus cisplatin combination treatment on tumor response is well supported by a median survival of 8.2 months. This compares favorably to a median survival of five months reported for each of three arms in a large randomized trial comparing FAM (5-FU, doxorubicin, and mitomycin-C), FA (5-FU, doxorubicin), and bolus 5-FU single-agent treatment [12]. Two randomised studies analysed the activity of single-agent gemcitabine in pancreatic cancer. One study demonstrated a significantly ($P = 0.0025$) longer overall survival for patients treated with gemcitabine (5.65 months) as compared to 5-FU (4.41 months) [3]. These data were confirmed by another trial showing again a significant ($P = 0.0001$) survival advantage for patients treated with single-agent gemcitabine (6.4 months) as compared to the matrix metalloproteinase inhibitor BAY12-9566 (3.2 months) [13]. By comparison, a median survival of 4.8 months (95% CI: 4.5–5.1 months) was observed in 2,380 patients treated with gemcitabine alone in a treatment investigational new drug program [14].

While 5-FU alone resulted in a one-year survival of only 2%, single-agent gemcitabine [3] and gemcitabine plus cisplatin resulted in 18% and 27% one-year survival

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rates, respectively. These higher rates achieved with gemcitabine alone and with gemcitabine-cisplatin are impressive in that one-year survival, rather than median survival, better represents the life gained in responding patients.

The comparatively long survival observed in our study may best be explained by the fact that a considerable number of patients (57%) had stable disease for ≥ 3 months, with a median time to progressive disease of 4.3 months. Of the patients with stable disease, six patients with stable disease survived for one year or more after start of treatment.

Additional efficacy assessments carried out in this study were improvement of disease-related symptoms reflected by the results from the QoL questionnaire, and changes from baseline in analgesic use and performance status. Disease-related symptom improvement was reported in 17% of patients after three cycles of gemcitabine treatment. The remaining 83% did not show an improvement in clinical status; however, the median survival of these patients was only 4.6 months. Nearly three-quarters of the patients noticed an improvement in pain, with a reduction or even omission of their analgesic requirements.

The gemcitabine plus cisplatin combination was rather well tolerated. Only five patients experienced WHO grade 3 or 4 toxicity, and no patients were discontinued from the study due to treatment-related toxicity. Hematological toxicity was moderate; only two patients experienced WHO grade 4 neutropenia and five patients experienced grade 4 thrombocytopenia. However, this was not accompanied by bleeding complications or severe infectious episodes. Thrombocytopenia was the main reason for reductions in cisplatin and gemcitabine doses, most of which occurred on day 15. Eleven percent of gemcitabine and 14% of cisplatin infusions had to be omitted, indicating that the treatment schedule chosen should not be intensified further.

There were only five cases of grade 3-4 nausea/vomiting, which were easily managed with standard antiemetics.

Other non-hematological toxicity was particularly infrequent and less than what was expected. Only one patient showed cisplatin-induced alopecia, and there were no reports of gemcitabine-induced flu-like symptoms. Pulmonary toxicity was not observed. A possible explanation for this low incidence of side effects might be the regular co-medication of dexamethasone for prevention of cisplatin-induced nausea and vomiting.

In summary, the combination of gemcitabine and cisplatin is a promising treatment option for patients with locally advanced and metastatic pancreatic cancer.

The combination treatment may be performed with few severe toxicities and without compromising quality of life. The favorable efficacy and mild toxicity profile of gemcitabine and cisplatin, together with the improvement of disease-related symptoms, analgesic use, and performance status, warrants further examination of this combination in a larger patient group. Therefore, a randomized phase III trial has been initiated to compare

the combination of gemcitabine and cisplatin *versus* single-agent treatment with gemcitabine in patients with pancreatic cancer.

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