

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO	
RAD: 12-129535- -8	FECHA: 2014-10-06 16:02:48
DEP: 2020 DIRECCION DE NUEVAS CREACIONES	EVE: 378 FASE NACIONAL INCLUIDO CAPITULO I
TRA: 11 PCT-PATENTE DE INVENCION CAPITULOS I Y II	FOLIOS: 28
ACT: 519 PRESENTACION	

DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado(a)/Señor(a)
JUAN PABLO CADENA SARMIENTO

Asunto: Radicación: 12-129535- -8
 Trámite: 11
 Evento: 378
 Actuación: 519
 Oficio: 12939
 Folios: 28

Patente de Invención	X			Patente de Modelo de Utilidad	
Vía Nacional					
Vía PCT (Fase Nacional)	X	Capítulo I	X	Capítulo II	
No. Solicitud Internacional	pct/us2011/025651				
Fecha de Presentación Internacional	22/02/2011				

1. Documentos estudiados

Descripción:	Radicado N°12-129535-00000-0000	Agosto 1 de 2012
Reivindicaciones	Radicado N°12-129535-00000-0000	Agosto 1 de 2012
	Radicado N°12-129535-00005-0000	Mayo 15 de 2013
Dibujos	Radicado N°12-129535-00000-0000	Agosto 1 de 2012
Secuencias	Radicado N°12-129535-00000-0000	Agosto 1 de 2012
Oposiciones	Radicado N°12-129535-00003-0000	Tecnoquímicas S.A. Abril 3 de 2013
	Radicado N°12-129535-00004-0000	Lafrancol S.A. Abril 4 de 2013
	Radicado N°12-129535-00007-0000	Tecnoquímicas S.A. Junio 24 de 2013
Prioridad:	US 61/307,095	Febrero 23 de 2010
	US 61/351,231	Junio 30 de 2010
	US 61/360,059	Junio 30 de 2010
	US 61/439,819	Febrero 4 de 2011

2. Análisis de la Prioridad

Se acepta la reivindicación de Prioridad porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

De acuerdo con lo establecido en el numeral 1.2.2.2 del Capítulo Primero del Título 10 de la Circular Única para efectos del examen de patentabilidad, se tendrá en cuenta la tasa pagada por el solicitante al momento de comenzar el examen para las reivindicaciones adicionales; esto es que cuando la solicitud contenga más de diez (10) reivindicaciones y no se haya pagado la tasa complementaria, sólo se estudiarán las cubiertas por la tasa pagada.

Se realizará el estudio de las reivindicaciones 1 a 14 presentes en el Radicado N°12-129535-00005-0000, porque se realizó el pago respectivo por las reivindicaciones adicionales 11 a 14, de acuerdo con el recibo presente en la página 152 del Radicado N°12-129535-00000-0000.

Título de la solicitud: “Terapia anti – angiogénesis para el tratamiento del cáncer ovárico”.

El problema planteado en esta solicitud consiste en la obtención de estrategias alternativas para el tratamiento del cáncer de ovario y de trompa de falopio.

Para resolver este problema técnico, la solicitud en estudio plantea la obtención de un kit que contiene un anticuerpo anti VEGF en combinación con otros agentes anticancerígenos, para el tratamiento del cáncer de ovario o de trompas de Falopio estadio III ó IV, que no hayan recibido tratamiento anterior.

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): C07K16/22.

4. Reivindicaciones relativas al uso o a un segundo uso (Art. 14 y 21 D 486)

El uso de las reivindicaciones 4, 10 y 14 no es patentable, de acuerdo con el artículo 14.

5. De la Solicitud de la Patente

Título

El título de la presente solicitud no se considera adecuado, puesto que este hace referencia directa a un método de tratamiento y a un uso determinado, los cuales se consideran como materia no patentable. Se solicita modificar el título de la solicitud.

Reivindicaciones (Art 30 D 486, Art 22 PCT)

Las reivindicaciones 1 y 11 no son claras, porque al mencionar un kit que contiene un “anticuerpo anti VEGF”, “un taxano” y “seguido por VEGF”, se pueden incluir muchos anticuerpos posibles que tienen función anti VEGF, así como se puede incluir cualquier compuesto derivado de taxano. Por lo tanto, se solicita mencionar de manera específica el anticuerpo anti VEGF (por la secuencia que lo define), así como se solicita definir el compuesto específico derivado de taxol. Adicionalmente, se solicita eliminar el enunciado “para tratar el cáncer ovárico, de trompa de falopio, o peritoneal no tratado anteriormente en una paciente humana”, porque denota el uso del kit mencionado y por lo tanto, el uso no se considera patentable. También se solicita eliminar la frase “en donde las instrucciones indican que la sobrevida sin progreso para los pacientes que reciben terapia de taxano y terapia de carboplatino y bevacizumab se extiende efectivamente en comparación con

otros pacientes ni tratados con bevacizumab”, debido a que esta expresión denota un resultado a alcanzar, dado que no solo se incluye la solución planteada por la solicitud, sino las soluciones alternativas presentes y futuras que conducen a obtener el mismo resultado. Por último, se solicita definir el kit de partes se debe definir de acuerdo a las características técnicas que consiste en describir las composiciones que contienen los principios activos, así como se debe describir los contenedores y dispositivos específicos que permiten que las composiciones de cada uno de los principios activos interactúen en un mismo sistema de entrega y permita diferenciar el kit mencionado de una simple administración por separado de cada uno de las composiciones.

Se solicita eliminar la reivindicación 5, porque menciona los mismos resultados a alcanzar objetados anteriormente para la reivindicación 1 y porque un kit no se puede caracterizar en función de las instrucciones de manejo e indicaciones.

Las reivindicaciones 6 y 7 se consideran como un resultado a alcanzar, porque no solo se incluye la solución planteada en la solicitud, sino que también se incluyen adicionalmente las posibles alternativas presentes y futuras que conducen a obtener el mismo resultado. Se solicita eliminar estas reivindicaciones.

Se solicita eliminar las reivindicaciones 8, 9, 12 y 13, porque replican la materia descrita en reivindicaciones anteriores.

Descripción (Art 28 D 486)

La descripción no es clara ni divulga el objeto de la solicitud de manera completa ni suficiente, porque la información que contiene no permite que una persona normalmente versada en la materia pueda comprender el problema técnico y la solución aportada ni permite ejecutarla o reproducirla, dado que a pesar de mencionar la presencia de kits que contienen anticuerpos anti VEGF en combinación con otros agentes quimioterapéuticos, el desarrollo de la invención menciona un método de tratamiento que involucra la administración de los compuestos mencionados anteriormente, mas no se orienta a la obtención de un kit (el cual debe contener los compuestos bajo un mismo sistema de entrega farmacéutico). Se solicita realizar las respectivas aclaraciones. Adicionalmente, existen párrafos dentro de la descripción que se encuentran en inglés, teniendo en cuenta que la legislación contempla que la descripción debe estar completamente en idioma castellano.

6. Análisis de Oposiciones

Argumentos de Tecnoquímicas S.A.

La sociedad opositora afirma que la solicitud en estudio se refiere al tratamiento de enfermedades con anticuerpos anti VEGF, lo cual no cumple con requisitos de patentabilidad, por cuanto la solicitud se caracteriza principalmente por la administración de un anticuerpo anti VEGF y otra quimioterapia adicional. En este sentido, el objeto de la solicitud no es patentable, de acuerdo con el Artículo 20 de la Decisión 486 en el literal d.

Adicionalmente el método se basa en la administración de medicamentos conocidos como lo es el Bevacizumab, un anticuerpo anti VEGF, que cuenta con la patente US6054297 del 25 de abril de 2000. La solicitud en estudio incumple con requisitos de claridad, dado que esta solicitud refiere un kit que comprende un envase que contiene una composición anticuerpo e instrucciones para el empleo de la composición, mencionando posteriormente una combinación con otros agentes manifestando la obtención de un efecto técnico.

La sociedad opositora afirma que el objeto de la solicitud en estudio carece de Novedad y de Nivel Inventivo, de acuerdo a los siguientes documentos que comprenden el estado de la técnica que antecede a la solicitud:

El artículo “Phase II study of carboplatin, paclitaxel and bevacizumab with maintenabce bevacizumab as first – line chemotherapy for advanced mullerian tumors” (Person et al) publicado el 1 de enero de 2010, describe un estudio que comprende un régimen terapéutico integrado por carboplatino, paclitaxel y bevacizumab, seguido de una terapia de mantenimiento, como tratamiento de primera línea para el cáncer de ovario (Pág. 155, párr. 1; pág. 159).

Por otra parte, el artículo “Combination gemcitabine, platinum and bevacizumab for the treatment of recurrent ovarian cáncer” (Richardson et al) publicado el 1 de diciembre de 2008, describe un régimen terapéutico que comprende gemcitabina, bevacizumab y un derivado de platino (cisplatino o carboplatino) para el tratamiento del cáncer de ovario, obteniendo una mejora en la sobrevivencia y en la respuesta debido al tratamiento divulgado, de tal manera que no solo se divulga el tratamiento, sino el efecto técnico que se obtiene mediante el mismo (Pág. 463, tabla 2).

Argumentos de Lafrancol S.A.

La sociedad opositora afirma que las composiciones y combinaciones farmacéuticas que se refieren a anticuerpos anti VEGF, incluido bevacizumab en combinación con otros agentes antitumorales para el tratamiento del cáncer de ovario, son prácticas y eventos totalmente conocidos en la industria farmacéutica, ya que no existe novedad ni nivel inventivo para las combinaciones que involucran moléculas totalmente conocidas en el sector químico farmacéutico, para lo cual no se puede otorgar un beneficio patentario sobre moléculas como bevacizumab, carboplatino o gemcitabina, las cuales cuentan con su beneficio patentario. También la sociedad opositora afirma que el objeto de la solicitud no se puede considerar como una invención, sino un descubrimiento, por cuanto el sinergismo obtenido por la combinación de dos o más agentes farmacológicamente activos se observa dentro de un organismo mediante ensayos clínicos. Finalmente, el objeto de la presente solicitud ha sido divulgado en los artículos “Phase II study of carboplatin, paclitaxel and bevacizumab with maintenabce bevacizumab as first – line chemotherapy for advanced mullerian tumors” (Person et al) y “Combination gemcitabine, platinum and bevacizumab for the treatment of recurrent ovarian cáncer” (Richardson et al).

Respuesta del solicitante

La sociedad Genentech, Inc. no realiza ningún pronunciamiento con respecto a las oposiciones y documentos expuestos por las sociedades opositoras Tecnoquímicas S.A. y Lafrancol S.A. La sociedad solicitante presenta un pliego reivindicatorio modificado, de tal manera que se restringe el objeto de protección de la solicitud en estudio.

Respuesta del Examinador Técnico

Después de la revisión de los argumentos presentados por las sociedades opositoras Tecnoquímicas S.A. y Lafrancol S.A., con respecto a la modificación del capítulo reivindicatorio propuesta por la sociedad Genentech, Inc., este Despacho considera en primer lugar que el objeto de la solicitud no define materia patentable, dado que a pesar de que la solicitud menciona un kit que contiene un anticuerpo anti VEGF (bevacizumab) en combinación con carboplatino y otro agente anticancerígeno seleccionado de paclitaxel o gemcitabina, el desarrollo de

la invención de acuerdo al memorial descriptivo conduce a divulgar un método de tratamiento consistente en la administración de los agentes anticancerígenos mencionados para una paciente que padece cáncer de ovario, es decir, no se define un kit que contenga los principios activos en una misma o en diferente composición bajo un mismo sistema de entrega; en segundo lugar, efectivamente los documentos referidos en las oposiciones mencionan la combinación de bevacizumab con agentes antineoplásicos como carboplatino, gemcitabina o un taxano, a partir de las cuales se obtiene el efecto técnico de mejorar la tasa de sobrevivencia y de respuesta al tratamiento, de tal manera que anticipa plenamente el objeto de la solicitud en estudio, objetando la novedad y el nivel inventivo. Por lo tanto, este Despacho declara fundadas las oposiciones presentadas por las sociedades Tecnoquímicas S.A. y Lafrancol S. A.

En conclusión, los documentos “Phase II study of carboplatin, paclitaxel and bevacizumab with maintenabce bevacizumab as first – line chemotherapy for advanced mullerian tumors” (Person et al) y “Combination gemcitabine, platinum, and bevacizumab for the treatment of recurrent ovarian cáncer” (Richardson et al), presentes en las oposiciones, desvirtúan la novedad y el nivel inventivo de la solicitud en estudio, por lo cual será tenido en cuenta dentro del Examen de Patentabilidad.

7. Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de solicitud de prioridad: Febrero 23 de 2010.

Consultadas las fuentes de información con que se cuenta, se encontraron los siguientes documentos que anticipa el objeto de esta solicitud:

Ítem	Documento	Título	Fecha de Publicación
D1	<i>Journal of Clinical Oncology</i> . 2010. 28 (1); 154 – 159	“Phase II Study of Carboplatin, Paclitaxel, and Bevacizumab With Maintenance Bevacizumab As First-Line Chemotherapy for Advanced Müllerian Tumors”	01/Enero/2010
D2	<i>International Journal of Gynecological Cancer</i> . 2007. 17 (4); 771 – 776	“A phase II study of outpatient first-line paclitaxel, carboplatin, and bevacizumab for advanced-stage epithelial ovarian, peritoneal, and fallopian tube cancer”	05/Marzo/2007
D3	<i>Gynecological Oncology</i> . 2008. 111 (3); 461 – 466	“Combination gemcitabine, platinum, and bevacizumab for the treatment of recurrent ovarian cancer”	01/Diciembre/2008
D4	US2008/0299116	“Vascular endothelial cell growth factor antagonist and uses thereof”	04/Diciembre/2008

El documento D1¹ divulga una combinación que contiene bevacizumab, paclitaxel y carboplatino, para el tratamiento del cáncer de ovario (Pág. 155, col. izq., ln. 23 – 27; col. der., ln. 19 – 25).

El documento D2² divulga una combinación que comprende bevacizumab, paclitaxel y carboplatino como terapia de inducción del cáncer de ovario en estado avanzado (Pág. 771, abstract).

El documento D3³ divulga una combinación que comprende bevacizumab, gemcitabina y carboplatino para el tratamiento del cáncer de ovario (Pág. 461, abstract).

El documento D4⁴ divulga compuestos polipéptidos antagonistas VEGF para el

1 <http://jco.ascopubs.org/content/28/1/154.full.pdf+html>
2 http://journals.lww.com/ijgc/Abstract/2007/07000/A_phase_II_study_of_outpatient_first_line.3.aspx
3 <http://www.sciencedirect.com/science/article/pii/S0090825808006525>
4 <http://worldwide.espacenet.com/publicationDetails/originalDocument?>

diagnóstico y tratamiento de enfermedades relacionadas con el incremento de angiogénesis (Pág. 1, párr. [0002]).

8. Examen de Patentabilidad

Novedad (Art 16 D 486)

La reivindicación 1 divulga “*Kit para tratar el cáncer ovárico... que comprende un envase que contiene una composición de un anticuerpo anti VEGF e instrucciones en combinación con un taxano y carboplatino...*” (Pág. 4 del radicado N° 12-129535-00005-0000).

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Solicitud	D1
Kit	Una combinación (Pág. 155, col. der., ln. 19 – 25)
Comprende un envase que contiene un anticuerpo anti VEGF	Comprende bevacizumab en NaCl 0.9% (Pág. 155, col. der., ln. 26)
Comprende un taxano	Comprende paclitaxel (Pág. 155, col. der., ln. 19 – 25).
Comprende carboplatino	Comprende carboplatino (Pág. 155, col. der., ln. 19 – 25).

Las características técnicas esenciales del objeto de la reivindicación 1, han sido divulgados previamente en el documento D1 (D1: Pág. 154, abstract; pág. 155, col. der., ln. 19 – 26) donde se menciona una combinación que contiene bevacizumab, paclitaxel y carboplatino para el tratamiento del cáncer de ovario y de trompas de falopio.

También el documento D1 menciona una terapia de mantenimiento de bevacizumab (Pág. 151, abstract, ver conclusión). Aunque la solicitud menciona un kit de partes, este no se encuentra correctamente definido, dado que el kit de la solicitud únicamente se refiere a un envase que contiene el anticuerpo anti VEGF mas instrucciones en combinación con un taxano y carboplatino, pero no se hace referencia si el taxano y el carboplatino están incluidos dentro del mismo envase en mezcla con el anticuerpo anti VEGF (lo que sería una composición farmacéutica) o si estos compuestos se encuentran físicamente separados en composiciones farmacéuticas diferentes, pero contienen un mismo sistema de entrega de los fármacos (kit de partes), por lo que el objeto de la solicitud en estudio se configura como una combinación referida a un método de tratamiento.

En consecuencia, la reivindicación 1, de acuerdo con lo divulgado en el documento D1, carece de Novedad.

Las reivindicaciones 3, 5 a 7, 9 y 12, dependientes de la reivindicación 1, no divulgan características adicionales que otorguen novedad a los compuestos de la presente solicitud. Por lo tanto, estas reivindicaciones también carecen de Novedad.

La reivindicación 1 divulga “*Kit para tratar el cáncer ovárico... que comprende un envase que contiene una composición de un anticuerpo anti VEGF e instrucciones en combinación con un taxano y carboplatino...*” (Pág. 4 del radicado N° 12-129535-00005-0000).

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

CC=US&NR=2008299116A1&KC=A1&FT=D&ND=3&date=20081204&DB=worldwide.espacenet.com&locale=es_LP

Solicitud	D2
Kit	Una combinación (Pág. 772, col. der., ln. 10 – 18)
Comprende un envase que contiene un anticuerpo anti VEGF	Comprende bevacizumab (Pág. 772, col. der., ln. 15 – 18)
Comprende un taxano	Comprende paclitaxel (Pág. 772, col. der., ln. 10 – 14).
Comprende carboplatino	Comprende carboplatino (Pág. 772, col. der., ln. 10 – 14).

Las características técnicas esenciales del objeto de la reivindicación 1, han sido divulgados previamente en el documento D2 (D1: Pág. 772, col. der., ln. 10 – 18) donde se menciona una combinación que contiene bevacizumab, paclitaxel y carboplatino para el tratamiento del cáncer de ovario y de trompas de falopio.

Tal como se mencionó anteriormente, aunque la solicitud menciona un kit de partes, el kit de la solicitud menciona solo un envase que contiene el anticuerpo anti VEGF e instrucciones en combinación con un taxano y carboplatino, pero no se refiere si conforman una composición farmacéutica o si estos compuestos se encuentran en composiciones farmacéuticas diferentes pero dentro de un solo sistema de entrega farmacéutico, por lo que el objeto de la solicitud en estudio se configura como una combinación referida a un método de tratamiento.

En consecuencia, la reivindicación 1, de acuerdo con lo divulgado en el documento D2, carece de Novedad.

Las reivindicaciones 3, 5 a 7, 9 y 12, dependientes de la reivindicación 1, no divulgan características adicionales que otorguen novedad a los compuestos de la presente solicitud. Por lo tanto, estas reivindicaciones también carecen de Novedad.

La reivindicación 11 divulga “*Kit para tratar el cáncer ovárico... que comprende un envase que contiene una composición de un anticuerpo anti VEGF e instrucciones en combinación con un gemcitabina y carboplatino...*” (Pág. 6 del radicado N° 12-129535-00005-0000).

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Solicitud	D3
Kit	Una combinación (Pág. 155, col. der., ln. 19 – 25)
Comprende un envase que contiene un anticuerpo anti VEGF	Comprende bevacizumab (Pág. 462, col. izq., ln. 10)
Comprende gemcitabina	Comprende gemcitabina (Pág. 462, col. izq., ln. 11 – 12)
Comprende carboplatino	Comprende carboplatino (Pág. 462, col. izq., ln. 11 – 12)

Las características técnicas esenciales del objeto de la reivindicación 11, han sido divulgados previamente en el documento D3 (D3: Pág. 461, abstract; pág. 462, col. izq., ln. 10 – 12; pág. 463, col. izq., ln. 40 – 42) donde se menciona una combinación que contiene bevacizumab, gemcitabina y carboplatino para el tratamiento de cáncer pulmón de células pequeñas, cáncer de ovario y de trompas de falopio.

Aunque esta reivindicación se refiere a un kit de partes, este no se encuentra correctamente definido, dado que el kit de la solicitud únicamente se refiere a un envase que contiene el anticuerpo anti VEGF mas instrucciones en combinación

con gemcitabina y carboplatino, pero no se hace referencia si la gemcitabina y el carboplatino están incluidos dentro del mismo envase en mezcla con el anticuerpo anti VEGF (lo que sería una composición farmacéutica) o si estos compuestos se encuentran físicamente separados en composiciones farmacéuticas diferentes, pero contienen un mismo sistema de entrega de los fármacos (kit de partes), por lo que el objeto de la solicitud en estudio se configura como una combinación referida a un método de tratamiento.

En consecuencia, la reivindicación 11, de acuerdo con lo divulgado en el documento D3, carece de Novedad.

Las reivindicación 13, dependiente de la reivindicación 11, no divulga características adicionales que otorguen novedad a los compuestos de la presente solicitud. Por lo tanto, estas reivindicaciones también carecen de Novedad.

Nivel Inventivo (Art 18 D 486)

La reivindicación 2 divulga “El kit de la reivindicación 1, en donde el anticuerpo anti – VEGF tiene una región variable de cadena pesada que comprende la SEQ ID N° 1 y una región variable de la cadena ligera que comprende la SEQ ID N° 2” (Pág. 4 del radicado N° 12–129535–00005–0000).

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Solicitud	D1	D3
Kit	Una combinación (Pág. 155, col. der., ln. 19 – 25)	Kit (Pág. 17, párr. [0178])
Comprende un envase que contiene un anticuerpo anti VEGF que comprende una región variable de cadena pesada (SEQ ID N° 1) EVQLVESGGG LVQPGGSLRL SCAASGYTFT NYGMNWRQA PGKGLEWVGW INTYTGPTY AADFRRFTF SLDTSKSTAY LQMNSLRAED TAVYYCAKYP HYGSSHWYF DVWGQGLVT VSS Y una región variable de cadena ligera (SEQ ID N° 2) DIQMTQSPSS LSASVGDRVT ITCSAQDIS NYLNWYQQKPKAPKVLIIYF TSSLHSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YSTVPWTFGQ GTKVEIKR	Comprende bevacizumab en NaCl 0.9% (Pág. 155, col. der., ln. 26)	Contiene un anticuerpo anti VEGF que comprende una región variable de la cadena pesada (Pág. 26, SEQ ID N°9) EVQLVESGGG LVQPGGSLRL SCAASGYDFT NYGMNWRQA PGKGLEWVGW INTYTGPTY AADFRRFTF SLDTSKSTAY LQMNSLRAED TAVYYCAKYP YYYGRSHWYF DVWGQGLVT VSSASTKGPS VFPLAPSSKS TSGGTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLS VVTPVSSSLG TQTYICNVNH KPSNTKVDKK VEPKSCDKTH L Y una región variable de cadena ligera (Pág. 21, SEQ ID N° 1) DIQLTQSPSS LSASVGDRVT ITCSAQDIS NYLNWYQQKPKAPKVLIIYF TSSLHSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YSTVPWTFGQ GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNIFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYLSSTLT LSKADYEKKH VYACEVTHQG LSSPVTKSFN RGEK
Comprende un taxano	Comprende paclitaxel (Pág. 155, col. der., ln. 19 – 25).	No se menciona
Comprende carboplatino	Comprende carboplatino (Pág. 155, col. der., ln. 19 – 25).	No se menciona

El documento D1 se considera el estado de la técnica más cercano al objeto de la solicitud de acuerdo con la reivindicación 2, porque se menciona una combinación que contiene bevacizumab, paclitaxel y carboplatino para el tratamiento del cáncer de ovario y de trompas de Falopio (Pág. 155, col. der., ln. 19 – 26).

La diferencia entre el kit de la solicitud con respecto a la combinación divulgada en el documento D1, radica en que el anticuerpo anti VEGF de la solicitud está caracterizado porque la región variable de la cadena pesada comprende la SEQ ID N° 1 y la región variable de la cadena ligera comprende la SEQ ID N° 2, mientras que en el documento D1 el anticuerpo VEGF corresponde a bevacizumab.

Esta diferencia no parece conceder un efecto técnico inesperado o superior a los compuestos de la fórmula I de la presente solicitud con respecto a los compuestos descritos en el documento D1, porque al comparar la proporción de supervivencia, la combinación descrita en el documento D1 (Pág. 158, fig. 2) es mucho mejor si se compara con la proporción de supervivencia obtenida por la combinación de la solicitud, de acuerdo con lo descrito en la figura 5.

El problema técnico objetivo que se pretende resolver es el siguiente: Cómo modificar la combinación divulgada para obtener un kit alternativo que contenga compuestos que sean administrados a pacientes con cáncer de ovario y de trompas de falopio que no hayan recibido tratamiento alguno.

El documento D3 divulga un kit que contiene una composición donde el principio activo es un anticuerpo anti VEGF, el cual comprende una región variable de cadena pesada definido en la SEQ ID N° 9 (ver subrayado) y una región variable de cadena ligera de la SEQ ID N° 1 (ver subrayado), los cuales presentan homología del 100% con respecto a las SEQ ID N° 1 y SEQ ID N° 2 del anticuerpo de la solicitud (Pág. 17, párr. [0178]; pág. 21, SEQ ID N° 1; pág. 26, SEQ ID N° 9).

Por lo tanto, una persona normalmente versada en la materia y conocedora de los conceptos mencionados en los documentos D1 y D3, sin ningún esfuerzo, modificaría la combinación descrita en el documento descritos en el documento D1, incluyendo la conformación de kit que comprende el anticuerpo anti VEGF sugerido en el documento D3, para obtener el kit propuesto en la solicitud de manera obvia o evidente.

En consecuencia, la reivindicación 2, de acuerdo con los documentos D1 y D3, carece de Nivel Inventivo.

Las reivindicaciones 3, 5 a 9, 12 y 13, dependientes de la reivindicación 1, no divulgan características técnicas adicionales que confieran nivel inventivo a los compuestos de la reivindicación 1, teniendo en cuenta que el documento D1 anticipa la combinación de la solicitud, donde el anticuerpo anti VEGF es bevacizumab. Por lo tanto, estas reivindicaciones, también carecen de Nivel Inventivo.

9. Conclusión

Los requisitos de Patentabilidad de esta solicitud se ven afectados de la siguiente manera:

Ite m	Documento	Reivindicaciones	Requisitos que afecta
D1	<i>Journal of Clinical Oncology</i> . 2010. 28 (1); 154 – 159	1, 3, 5 a 7, 9, 12 y 13	Novedad
		2, 3, 5 a 9 y 12 a 13	Nivel Inventivo
D2	<i>International Journal of Gynecological Cancer</i> . 2007. 17 (4); 771 – 776	1, 3, 5 a 7, 9, 11 y 13	Novedad
D3	<i>Gynecological Oncology</i> . 2008. 111 (3); 461 – 466	11 y 13	Novedad
D4	US2008/0299116	2, 3, 5 a 9, 12 y 13	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir del día siguiente de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante de sesenta (60) días para dar respuesta a este requerimiento y presentarla por escrito.

Finalmente, se le recuerda al solicitante que si como respuesta a este requerimiento llegara a modificar el capítulo reivindicatorio y éste contenga más de diez (10) reivindicaciones, no pagará la tasa de modificación voluntaria pero sí la correspondiente al pago por reivindicación adicional.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha 2014-10-14

Elaboró: Dayron Alexander Ramirez Reyes
Revisó: Consuelo Leguizamon Leguizamon

Phase II Study of Carboplatin, Paclitaxel, and Bevacizumab With Maintenance Bevacizumab As First-Line Chemotherapy for Advanced Müllerian Tumors

Richard T. Penson, Don S. Dizon, Stephen A. Cannistra, Maria R. Roche, Carolyn N. Krasner, Suzanne T. Berlin, Neil S. Horowitz, Paul A. DiSilvestro, Ursula A. Matulonis, Hang Lee, Modjule A. King, and Susana M. Campos

From the Dana-Farber/Harvard Cancer Center; Massachusetts General Hospital; Dana-Farber Cancer Institute; Beth Israel Deaconess Medical Center, Boston, MA; and Women and Infants' Hospital, Providence, RI.

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Clinical Trials repository link available on JCO.org.

Corresponding author: Richard T. Penson, MD, MRCP, Division of Hematology Oncology, Yawkey 9-064, Massachusetts General Hospital, 32 Fruit St, Boston MA 02114; e-mail: rpenson@partners.org.

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ABSTRACT

Purpose

New strategies are needed to improve outcomes for patients with advanced ovarian cancer. Bevacizumab is a recombinant humanized monoclonal antibody that neutralizes vascular endothelial growth factor but is associated with GI perforations (GIPs) in patients with recurrent disease.

Patients and Methods

An open-label, phase II clinical trial was conducted in newly diagnosed patients with stage $\geq$ IC epithelial müllerian tumors. Patients received intravenous (IV) carboplatin (area under the curve = 5), paclitaxel (175 mg/m² IV), and bevacizumab (15 mg/kg IV) for six to eight cycles on day 1 every 21 days. Bevacizumab was omitted in the first cycle and continued as a single agent for 1 year.

Results

Sixty-two women participated in this study. Fifty-one patients (82%) were optimally surgically cytoreduced before treatment. The median age was 58 years (range, 18 to 77 years). Forty-five women (73%) had ovarian cancer, 10 (16%) had peritoneal cancer, four (6%) had fallopian tube cancers, and three (5%) had uterine papillary serous tumors. The majority of patients (90%) had stage III or IV disease. A median of 17 maintenance cycles (range, 0 to 25+ cycles) of bevacizumab (556 cycles) were administered with mild toxicity. Treatment was associated with two pulmonary embolisms and two GIPs, all occurring during the chemotherapy phase of treatment (364 total cycles). No grade 4 toxicities were seen during maintenance bevacizumab treatment. Radiographic responses were documented in 21 (75%) of 28 women with measurable disease (11 complete responses and 10 partial responses), with CA-125 responses in 76% of patients (11 complete responses, 21%; and 35 partial responses, 55%). The progression-free survival rate at 36 months was 58%.

Conclusion

The regimen of carboplatin, paclitaxel, and bevacizumab with maintenance bevacizumab is feasible, safe, and worthy of future study in advanced ovarian cancer.

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INTRODUCTION

Ovarian cancer is diagnosed in approximately 22,400 American women each year, and 15,000 women with ovarian cancer die, making it the leading cause of death from gynecologic malignancies in the United States.¹ Difficult to detect, the disease typically presents with symptoms only when advanced.² However, ovarian cancer is among the most sensitive of solid tumors to chemotherapy. The combination of carboplatin and paclitaxel is widely considered to be standard first-line therapy.³ Survival has improved little since the introduction of platinum, and taxane and biologics combined with this regimen are being explored in the hope of improving outcomes.⁴

Ovarian cancers secrete large amounts of vascular endothelial growth factor (VEGF) in vitro and in vivo. VEGF seems to play a crucial role in angiogenesis and tumor-induced immunosuppression in ovarian cancer patients⁵ and has been confirmed as an independent prognostic indicator by multivariate analysis of survival.⁶

Bevacizumab (Avastin; Genentech, South San Francisco, CA) is a recombinant humanized monoclonal antibody directed to VEGF⁷ that binds to and neutralizes the biologic properties of human VEGF.⁸ A phase II study conducted by the Gynecologic Oncology Group (GOG) evaluated bevacizumab monotherapy in women with recurrent platinum-resistant ovarian cancer and demonstrated a

response rate of 21% and a 6-month progression-free survival (PFS) rate of 40%.⁹ A separate consortium study of the combination of bevacizumab with daily, low-dose, oral cyclophosphamide demonstrated similar findings.¹⁰ However, a company-sponsored study was halted prematurely with a high rate (11%) of GI perforation (GIP).¹¹

Paclitaxel, carboplatin, and bevacizumab have been combined in lung cancer, but it is unknown whether the feasibility of this regimen will be generalizable to other diseases. This is especially important because we know that bevacizumab by itself can cause GIP in recurrent ovarian cancer and can be life threatening. Thus, the full toxicity of bevacizumab cannot always be extrapolated from one disease to another. Furthermore, it has been proposed that the earlier use of bevacizumab, when there is less bulky disease, especially after chemical debulking with one cycle of chemotherapy, might be better tolerated, with less risk of GIP. Therefore, the present study was designed to test the feasibility of the regimen in newly diagnosed ovarian cancer to determine whether the toxicity profile, especially with respect to GIP, would be acceptable enough to justify moving it into a phase III trial. The results of the present study provide a firm basis for the ongoing phase III trial (GOG218), which also tests the hypothesis tested in this study that protracted bevacizumab may impact PFS.

PATIENTS AND METHODS

The primary objectives of this multi-institutional phase II study were to examine the toxicity of this treatment when administered in adjuvant fashion and estimate the objective response rate and PFS of carboplatin, paclitaxel, and bevacizumab followed by single-agent bevacizumab as consolidation for advanced müllerian tumors.

Patients

The study was an investigator-initiated study approved by the Dana-Farber/Harvard Cancer Center (DF/HCC; Boston, MA) Scientific Review Committee and Institutional Review Board. The study was conducted at four sites in compliance with institutional and federal guidelines. Patients were eligible if they met the following criteria and signed written informed consent: ≥ 18 years old; histologic diagnosis of epithelial ovarian carcinoma, fallopian tube cancer, primary peritoneal carcinoma, or papillary serous müllerian carcinoma; a previous attempt at surgical debulking; stage $\geq$ IC; Eastern Cooperative Oncology Group performance status of 0 to 2; peripheral neuropathy less than grade 2; and life expectancy ≥ 6 months. Patients meeting any of the following criteria were not eligible for the trial: a history of serious systemic disease, myocardial infarction within the last 6 months, uncontrolled hypertension, unstable angina, New York Heart Association grade 2 or greater congestive heart failure, unstable symptomatic arrhythmia requiring medication (patients with chronic atrial arrhythmia, ie, atrial fibrillation or paroxysmal supraventricular tachycardia, were eligible), or peripheral vascular disease (grade ≥ 2); prior history of thrombotic events or stroke; prior chemotherapy or radiotherapy; bleeding diathesis, therapeutic anticoagulation (prophylactic low-dose warfarin was allowed; 1 mg orally every day with international normalized ratio < 1.2), or any active bleeding; evidence of tumor involving major blood vessels on computed tomography (CT) scan; a surgical wound that had failed to close; prior treatment with an antiangiogenic agent; active psychiatric disease or neurologic symptoms requiring treatment (grade 1 sensory neuropathy was allowed); CNS or brain metastases; proteinuria or clinically significant impairment of renal function (patients unexpectedly discovered to have $> 1+$ proteinuria at baseline had to have < 1 g of protein/24 hours); dementia or significantly altered mental status that would prohibit the understanding and/or giving of informed consent; hypersensitivity to polyethoxylated castor oil (Cremophor EL; BASF, Ludwigshafen, Germany); active bacterial, viral, or fungal infections; or receiving other investigational therapy. Neutrophil count had to be more than $1,500/\mu\text{L}$,

and platelet count had to be more than $100,000/\mu\text{L}$. Alkaline phosphatase and bilirubin had to be less than $1.5\times$ the upper limit of normal, AST had to be less than $5\times$ the upper limit of normal, and calculated creatinine clearance had to be more than 50 mL/min. Patients could not be included if the initial surgical cytoreduction was such that interval cytoreductive surgery might materially improve prognosis because patients were not permitted to have interval cytoreductive surgery on study.

All patients were registered with the Quality Assurance for Clinical Trials group at DF/HCC who also managed all the data in a Health Insurance Portability and Accountability Act-compliant format. Patients were required to have a medical history and physical examination, with evaluation of performance status, CBC with differential and platelets, serum creatinine, total bilirubin, AST, ALT, and urinalysis before each cycle of treatment. Tumor response was evaluated using CA-125 and at least abdominopelvic CT every three cycles and every 3 months during maintenance until completion of study. The study competed with a DF/HCC study investigating intraperitoneal chemotherapy preferentially enrolling patients with optimally resected disease.

Treatment and Dose Modifications

Carboplatin and paclitaxel were administered concurrently with bevacizumab after surgery for six to eight cycles every 21 days. Bevacizumab was obtained directly from Genentech. Bevacizumab was omitted in the first cycle and immediately postoperatively and was continued for 1 year of maintenance therapy. Bevacizumab was suspended for 4 to 6 weeks before major surgery and 2 weeks before minor elective surgery.

Bevacizumab was diluted in 0.9% sodium chloride and administered initially over 90 minutes, with the rate subsequently increased as tolerated (minimum, 30 minutes). Patients received paclitaxel premedication with dexamethasone 20 mg orally 14 and 7 hours before paclitaxel administration, using an in-line filter with a microporous membrane not greater than $0.22\ \mu\text{m}$ over 3 hours. All sites used 12- and 7-hour dexamethasone premedication. Carboplatin was infused intravenously over 1 hour, with the dose calculated using the Calvert formula based on calculated creatinine clearance (Jelliffe formula). Carboplatin (area under the curve = 5) is an institutional standard and may allow the future incorporation of novel agents that have hematologic toxicity, but it was not anticipated that bevacizumab would exacerbate hematologic toxicity. Standard supportive care was used without primary growth factor prophylaxis.

Dose modifications for hematologic toxicities were based on blood counts at the time of re-treatment (re-treatment required absolute neutrophil count [ANC] $\geq 1,000/\mu\text{L}$ and platelets $\geq 100,000/\mu\text{L}$). For an ANC of 750 to $1,000/\mu\text{L}$, granulocyte colony-stimulating factor was added; drugs were held for ANC less than $750/\mu\text{L}$. For a platelet count of 60,000 to $99,000/\mu\text{L}$, carboplatin was reduced to area under the curve of 4; drugs were held for a platelet count of less than $60,000/\mu\text{L}$, with bevacizumab held for a platelet count of less than $75,000/\mu\text{L}$. Patients were removed from protocol if hematologic toxicity lasted more than 35 days. For nonhematologic toxicity, dose reductions of paclitaxel were sequentially allowed to $135\ \text{mg}/\text{m}^2$ and $100\ \text{mg}/\text{m}^2$ for neuropathy grade ≥ 2 , and one dose reduction of paclitaxel to $135\ \text{mg}/\text{m}^2$ was allowed for grade 2 liver toxicity. Bevacizumab infusion-related events were managed with premedication and slower infusions, and the drug was discontinued for any grade ≥ 3 toxicity and all arterial thromboembolic events.

Patients with grade 3 liver toxicity could have drug held until recovery to $\leq$ grade 1, with the drug discontinued if grade 3 liver function test elevations occurred with re-treatment. Proteinuria had to be less than $3+$ to allow treatment with bevacizumab, and $2+$ dipstick proteinuria required a 24-hour collection and drug to be held until proteinuria improved to less than 2 g of protein in a 24-hour urine collection. If this did not happen within 2 months or nephrotic syndrome developed (grade 4), bevacizumab was discontinued. Patients were taken off study for other grade 3 or 4 toxicity, and all arterial thromboembolic events. Patients who developed venous thromboembolism on study were allowed to continue with full anticoagulation if all of the following criteria were met: a stable in-range international normalized ratio (2 to 3), no prior grade 3 or 4 hemorrhagic event, and no tumor involving major blood vessels on any prior CT scan.

Toxicity

Toxicity was evaluated using Common Terminology Criteria for Adverse Events version 3. Serious adverse events were submitted to the US Food and Drug Administration, Genentech Drug Safety, and all participating investigators.

Response

PFS was estimated with CT scans and CA-125 blood tests every 3 months and measured from study registration. Response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST),¹² and CA-125 response was evaluated by Rustin criteria requiring two 50% reductions in CA-125.¹³

Statistical Considerations

Accrual was set at 62 patients. The study initially recruited 17 patients and was temporarily halted for evaluation of deaths as a result of thromboembolism, arterial complications, and GIPs. The study was to be terminated if five or more of these toxicities were observed. The probability of missing these toxicities was $P = .025$ when the true rate would have been 50% and was $P = .126$ when the true rate would have been 40%. The overall survival and PFS times were estimated using the Kaplan-Meier method, and 95% CIs were estimated using the exact binomial distribution.

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	Patients (N = 62)	
	No.	%
Age, years		
Median	58	
Range	18-77	
Follow-up, months		
Median	17	
Range	1-26	
Performance status		
1	42	68
2	20	32
Stage		
Early	6	10
III	43	69
IV	13	21
Site		
Ovary	45	73
Primary peritoneal	10	16
Fallopian tube	4	8
UPSC	3	5
Histology		
Papillary serous	43	69
MMMT	7	11
Mixed	6	10
Endometrioid	3	5
Clear cell	3	5
Grade		
3	50	81
2	7	11
1	3	5
Unknown	2	3
Cytoreduction*		
Optimal	49	79
Suboptimal	13	21

Abbreviations: UPSC, uterine papillary serous carcinoma; MMMT, malignant mixed Müllerian tumor.

*Suboptimal includes patients who did not get surgery because of stage IV disease (n = 3).

RESULTS

Patient Characteristics

Between March 2005 and February 2007, 62 eligible and evaluable patients were enrolled. All patients have completed all planned cycles of chemotherapy. A total of 364 cycles of chemotherapy and 556 cycles of consolidation were administered. Thirteen patients (21%) received more than six cycles of chemotherapy (five received seven cycles, and eight received eight cycles) for a persistently elevated but decreasing CA-125, with poor prognostic features.

Patient characteristics are listed in Table 1. Although in concept, the study was designed for suboptimally cytoreduced patients and there was a competing phase II study of intraperitoneal chemotherapy, many of the patients (79%) had optimally cytoreduced disease, reflecting the typical optimal cytoreduction rate of the institutions (approximately 80%) and thus a likely selection bias. However, CT scan was required before commencing chemotherapy, and the operative evaluation significantly underestimated residual disease, with many patients (45%) having baseline CT scans with measurable disease (> 1 cm on spiral CT) and thus suboptimal disease.

All patients were evaluable for toxicity, and 28 were evaluable for response (Fig 1). Two women (3%) withdrew consent; one patient, with a prior history of problematic diverticulitis, withdrew when the information about GIP became available, and the other patient wished to discontinue maintenance for an overdue hip replacement. Only two patients had second-look laparotomies, which were both negative and uncomplicated.

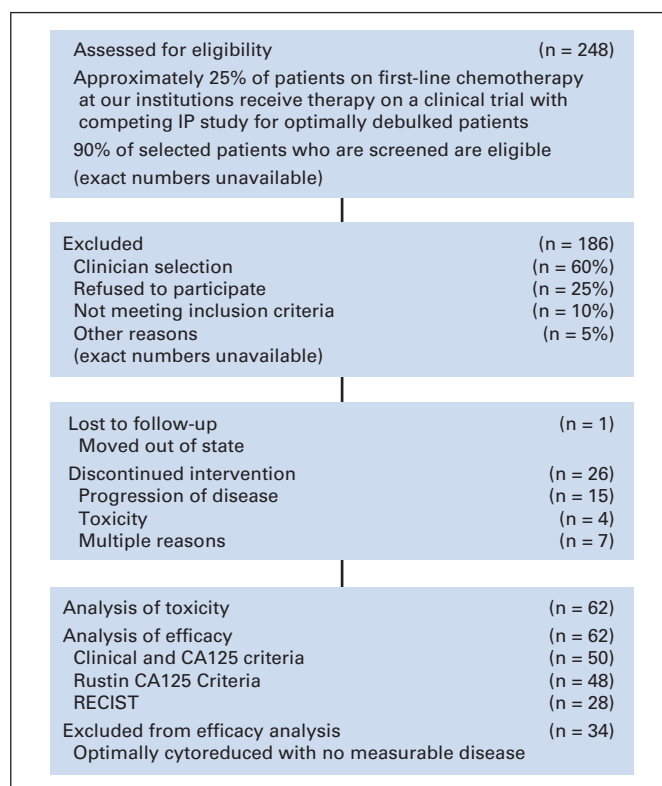


Fig 1. CONSORT diagram. RECIST, Response Evaluation Criteria in Solid Tumors.

Toxicity

Toxicities for the two phases (chemotherapy and single-agent bevacizumab treatment) of the study are listed in Tables 2 and 3. As expected, the combination of paclitaxel and carboplatin was generally well tolerated. There were no apparent excess chemotherapy toxicities because of the concurrent administration of bevacizumab.

Four women (6%) were removed for toxicity with autonomic neurotoxicity, hypertension, bilateral pulmonary embolism complicating a wound infection and empyema, and a nasal perforation. There were two wound healing delays, with both wounds not healing until the completion of chemotherapy, no arterial thromboses, no serious hemorrhages, and no treatment-related deaths. Allergic reactions were caused by bevacizumab (three grade 1 reactions in one patient) and paclitaxel ($n = 11$; five grade 3, two grade 2, and four grade 1 reactions in six patients) but not carboplatin.

On chemotherapy, eight patients required dose delays. Paclitaxel dose was reduced nine times in four patients, and carboplatin dose was reduced four times in three patients. During maintenance, there were 20 doses held in 14 patients.

Although hematologic toxicity was common, it was rarely complicated, and only two patients had fever and neutropenia. Granulocyte colony-stimulating factor was not proscribed in the protocol, which mandated dose delays and dose reductions, but five patients were administered filgrastim ($n = 1$) or pegfilgrastim. The episodes of severe thrombocytopenia with bevacizumab alone were late hematologic toxicity from carboplatin. Thromboses were documented in

Table 3. Consolidation Toxicity During 556 Cycles of Bevacizumab

Toxicity	Maximum Grade of Toxicity per Patient (No. of patients)				Total No. of Patients
	1	2	3	4	
Hematologic					
Neutropenia	3	1	1	0	5
Anemia	12	0	0	0	12
Thrombocytopenia	4	0	1	1	6
Nonhematologic					
Musculoskeletal pain*	25	14	3	0	42
Metabolic*	24	6	2	0	32
Bleeding	31	0	0	0	31
Fatigue	33	7	0	0	40
Rash or edema	9	2	0	0	11
Dysphonia	10	0	1	0	11
Hypertension	9	7	5	0	21
Proteinuria	4	5	2	0	11
Constitutional	3	0	0	0	3
Palpitations	2	0	0	0	1
Allergic reaction	1	0	0	0	1
Thromboembolism	0	0	0	0	0
GI perforation	0	0	0	0	0

NOTE. Additional grade 3 or 4 adverse events occurring in at least one instance were infection (grade 3, $n = 1$) and syncope (grade 3, $n = 1$). Toxicities were evaluated according to the Common Terminology Criteria for Adverse Events (version 3).

*Cumulative from various regions or sources.

Table 2. Chemotherapy Toxicity During 364 Cycles of Chemotherapy

Toxicity	Maximum Grade of Toxicity per Patient (No. of patients)				Total No. of Patients
	1	2	3	4	
Hematologic					
Neutropenia	7	4	4	10	25
Anemia	36	5	2	0	43
Thrombocytopenia	7	2	2	2	13
Febrile neutropenia	0	1	1	0	2
Nonhematologic					
Musculoskeletal pain*	34	12	3	0	49
Metabolic*	18	16	8	0	42
Hemorrhage	46	1	0	0	47
Alopecia	8	45	0	0	53
Neuropathy	31	6	4	0	41
Abnormal liver function tests	18	1	0	1	20
Cough or shortness of breath	18	2	0	0	20
Vomiting	13	5	2	0	20
Allergic reaction†	1	1	4	0	6
Hypertension	1	3	6	0	10
Thromboembolism	0	0	0	2	2
Palpitations	3	0	0	0	3
Proteinuria	5	1	0	0	6
GI perforation	1	0	0	1	2

NOTE. Additional grade 3 or 4 adverse events occurring in at least one instance were dehydration (grade 3, $n = 1$), fatigue (grade 3, $n = 1$), mucositis (grade 3, $n = 1$), and rash (grade 3, $n = 1$). Toxicities were evaluated according to the Common Terminology Criteria for Adverse Events (version 3).

*Cumulative from various regions or sources.

†All of the allergic reactions were to paclitaxel.

10% of patients but were readily managed with anticoagulation. Within months of starting the study, an amendment was filed to allow and encourage patients to take prophylactic aspirin during the consolidation phase of the study.

There were two GIPs. One patient presented with a pulmonary embolism, and on CT scan, a focus of gas was incidentally identified within mesenteric fat thought to be secondary to evolving infection or, less likely, an anastomotic leak, with no clinical sequelae. The other patient had a catastrophic GIP with surgery and received intensive care with pressor support for more than a week. No clear site of perforation was identified at laparotomy, with no persisting tumor identified by biopsy. Neither patient died. Patients with GIP and nephrotic syndrome were not kept on study.

Twenty-seven patients (44%) required antihypertensives (first-line lisinopril), but only two patients required multiple agents. One patient developed transient, fully reversible nephrotic syndrome. No patient developed reversible hypertensive leukoencephalopathy syndrome.

Patients discontinued or were removed from maintenance therapy for progressive disease ($n = 15$; 24%), toxicity ($n = 4$; 6%), or multiple other reasons ($n = 7$; 11%), with the most common reason cited being intolerable myalgias because they were moderate but continual (reported in 10% of patients).

Efficacy

Clinical outcomes are listed in Tables 4 and 5, and overall survival and PFS are illustrated in Figure 2. At the completion of chemotherapy, 96% (95% CI, 90% to 99%) of patients had achieved at least a partial response by clinical and radiologic criteria and had a normal CA-125 (< 35 U/mL). Combining RECIST and formal Rustin criteria, the overall response rate was 76% (95% CI, 69% to 87%), with a

Table 4. Response to Chemotherapy Including All Patients Who Completed More Than Two Cycles of Chemotherapy

Response	Patients		
	No.	%	95% CI
Clinical and CA-125 response (N = 62)	50	81	71 to 92
Rustin criteria (n = 50)			
Overall response	48	94	86 to 99
Complete response	38	75	62 to 87
Partial response	10	20	10 to 34
Stable disease	2	4	1 to 14
Progressive disease	0	0	0 to 7
RECIST (n = 60)			
Overall response	45	75	62 to 85
Complete response	14	23	13 to 36
Partial response	31	52	38 to 65
Stable disease	15	25	15 to 37
Progressive disease	0	0	0 to 6

NOTE. The upper clinical response rate reflects the number of patients in remission at the end of chemotherapy (no clinical evidence of disease and a normal CA-125; intent-to-treat analysis for the whole cohort). The stricter criteria for response (RECIST and Rustin criteria [two 50% reductions in CA-125]) are shown with the denominator. Two patients withdrew consent but are included in the intent-to-treat analysis despite not receiving bevacizumab because they agreed to be observed, 12 patients had initially normal CA-125 levels, and two patients did not get scans for evaluation because they withdrew from the study as a result of toxicity (pulmonary embolism and neuropathy).

Abbreviation: RECIST, Response Evaluation Criteria in Solid Tumors.

complete response documented in 13 patients (21%), partial response in 34 patients (55%), and stable disease in 13 patients (21%). No patient had progressive disease on chemotherapy.

Median PFS estimate is 29.8 months, and its lower 95% CI is 17.3 months, with the upper CI not yet estimable. Median overall survival has not yet been reached.

DISCUSSION

As the leading cause of death from gynecologic malignancies in the United States, ovarian cancer remains a silent killer of too many women, and the development of more effective therapy is the highest priority in gynecologic oncology. With increasing evidence that anti-

Table 5. Outcome on Maintenance Therapy (n = 58)

Response	No. of Patients	%
Removed from study prior to maintenance	4	6
Completed 18 cycles of maintenance therapy	29	47
Completed with increasing CA-125	2	3
Reason for removal from maintenance therapy		
Progressive disease	16	26
Multiple reasons*	7	11
Toxicity	4	6

NOTE. Percentages are based on the entire study population. Median progression-free survival estimate is 29.8 months, and its lower 95% CI is 17.3 months, with the upper CI not yet estimable. Median overall survival has not yet been reached.

*Five patients were removed from maintenance therapy at their or their clinician's discretion with stable disease, one patient was removed for a dental procedure, and one patient was lost to follow-up.

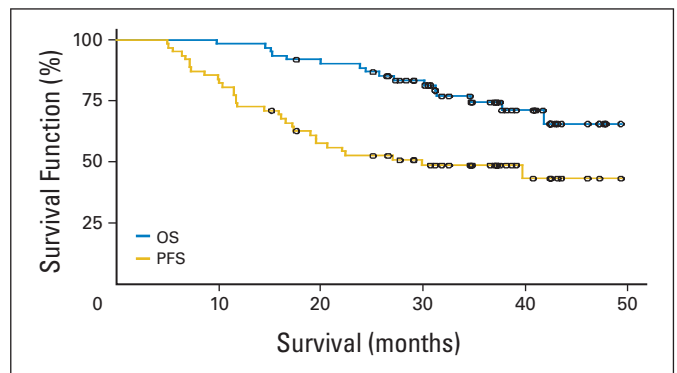


Fig 2. Overall survival (OS) and progression-free survival (PFS). Analysis includes all evaluable patients; two patients withdrew consent, 12 patients had initially normal CA-125 levels, and two patients did not get scans for evaluation.

angiogenic agents may be particularly potent in ovarian cancer, we have investigated the addition of bevacizumab with standard chemotherapy. We show here that the combination of carboplatin, paclitaxel, and bevacizumab is well tolerated and associated with a high remission rate. Although the intraperitoneal administration of chemotherapy is associated with better overall survival in carefully selected patients, in patients destined to experience relapse, intravenous carboplatin plus paclitaxel represents a convenient, well-tolerated regimen with a predictable toxicity profile that ideally lends itself to the integration of novel biologics.

In addition to the incorporation of bevacizumab with chemotherapy, we incorporated a maintenance phase of treatment using bevacizumab as a single agent. There are four main reasons to investigate protracted exposure to bevacizumab, despite the unproven benefit in this disease, extra risk, and cost. The first reason is mechanistic; the agent, although inducing apoptosis, is considered a biologic, and protracted exposure is thought to be necessary to maintain tumor dormancy. The second reason is preclinical; in the preclinical studies of ovarian cancer (SKOV-3 intraperitoneal murine model), the function-blocking VEGF antibody A4.6.1 significantly inhibited subcutaneous SKOV-3 tumor growth approximately 20-fold compared with controls ($P < .05$), and within 2 to 3 weeks of cessation of A4.6.1, mice developed severe ascites and tumor burden.¹⁴ The third reason is a clinical paradigm; studies in other solid tumors have treated patients until tumor progression, and it is now widely accepted that continual rather than intermittent palliative chemotherapy translates into a better quality of life.¹⁵ Finally, GOG178, a single prematurely closed but provocative randomized controlled trial, reported a large improvement in PFS.¹⁶ PFS is considered one of the most important end points in patients with advanced ovarian cancer. Despite these contentions, maintenance therapy should not be considered standard with supporting data from definitive randomized controlled trials.

Avoiding the risk of GIP remains a major priority for clinical investigations of bevacizumab in ovarian cancer. Our observed GIP rate (3%) approaches that observed in patients with metastatic colorectal cancer (2.4%).^{11,17-19} For patients with recurrent disease a number of strategies were identified to try and reduce the risk of GIP, including limiting the number of prior lines and excluding bowel involvement.²⁰ However, transmural metastases are common in recurrent disease, and the optimal and safest time to impact the clinical course of the disease may be during first-line therapy.

Micha et al²¹ report a similar overall response rate (80%) with an identical regimen of paclitaxel, carboplatin, and bevacizumab primary induction therapy in 20 similar patients, with similar toxicity. Traditionally, first-line clinical trials in ovarian cancer have not reported response rates because, after surgery, patients are considered to not have measurable disease. However, it is increasingly recognized that there is often evaluable and measurable disease in many patients who are surgically considered to have been optimally cytoreduced (< 1 cm disease at the end of surgery) if CT scans are performed before adjuvant chemotherapy. The outcomes of our study compare favorably with GOG158, which showed that carboplatin plus paclitaxel was not inferior to cisplatin plus paclitaxel in 792 patients.²²

First-line carboplatin, paclitaxel, and bevacizumab with maintenance bevacizumab is a highly active combination that remains experimental but is feasible in patients with previously untreated advanced ovarian cancer. Randomized controlled trials are required to determine the efficacy of bevacizumab when used in combination with chemotherapy and as maintenance therapy in the treatment of ovarian cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Conception and design: Richard T. Penson

Financial support: Richard T. Penson

Administrative support: Richard T. Penson, Maria R. Roche

Provision of study materials or patients: Richard T. Penson, Don S. Dizon, Stephen A. Cannistra, Carolyn N. Krasner, Suzanne T. Berlin, Neil S. Horowitz, Paul A. DiSilvestro, Ursula A. Matulonis, Susana M. Campos

Collection and assembly of data: Richard T. Penson, Maria R. Roche, Modjolie A. King

Data analysis and interpretation: Richard T. Penson, Stephen A. Cannistra, Hang Lee, Susana M. Campos

Manuscript writing: Richard T. Penson, Stephen A. Cannistra, Ursula A. Matulonis, Hang Lee, Susana M. Campos

Final approval of manuscript: Richard T. Penson, Don S. Dizon, Stephen A. Cannistra, Maria R. Roche, Carolyn N. Krasner, Suzanne T. Berlin, Neil S. Horowitz, Paul A. DiSilvestro, Ursula A. Matulonis, Hang Lee, Modjolie A. King, Susana M. Campos

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A phase II study of outpatient first-line paclitaxel, carboplatin, and bevacizumab for advanced-stage epithelial ovarian, peritoneal, and fallopian tube cancer

J.P. MICHA*, B.H. GOLDSTEIN*, M.A. RETTENMAIER*, M. GENESEN†, C. GRAHAM*, K. BADER*, K.L. LOPEZ*, M. NICKLE* & J.V. BROWN, III*

*Gynecologic Oncology Associates, Hoag Cancer Center, Newport Beach, California and

†Comprehensive Cancer Center at Desert Regional Medical Center, Palm Springs, California

Abstract. Micha JP, Goldstein BH, Rettenmaier MA, Genesen M, Graham C, Bader K, Lopez KL, Nickle M, Brown JV III. A phase II study of outpatient first-line paclitaxel, carboplatin, and bevacizumab for advanced-stage epithelial ovarian, peritoneal, and fallopian tube cancer. *Int J Gynecol Cancer* 2007;17:771–776.

The purpose of this study was to assess the response rate and toxicity of paclitaxel, carboplatin, and bevacizumab (PCB) primary induction therapy for the treatment of advanced-stage ovarian carcinoma. Twenty patients were treated with paclitaxel (175 mg/m²), carboplatin (AUC of 5 IV), and bevacizumab (15 mg/kg) of body weight; q21 days for six cycles. Bevacizumab was administered at cycles two through six. Patients received 116 cycles of PCB chemotherapy (median = 6, range 2–6) and were evaluable for toxicity assessment. Grade 3 and 4 neutropenia developed in 23.3% and 25% of cycles, with no incidence of grades 3/4 thrombocytopenia or anemia. Prior to cycle six, one patient was removed from the study due to grade 3 neuropathy and another patient was excluded due to clinical deterioration. There was no incidence of gastrointestinal perforations, and only two patients demonstrated grade 3 hypertension (HTN). No grade 4 HTN was observed. Eighteen patients were evaluated for response following induction therapy. Six demonstrated a complete response (30%) and ten exhibited a partial response (50%), resulting in a total response rate of 80%. One patient exhibited stable disease (5%), and one demonstrated disease progression (5%). The lack of bowel perforations and wound complications should mitigate some concerns regarding these side effects. This study suggests that first-line treatment with PCB can be safely administered to previously untreated advanced-stage ovarian carcinoma patients. The favorable toxicity results and reasonable response rate warrant additional study in a larger patient population.

KEYWORDS: bevacizumab, carboplatin, chemotherapy, gynecological oncology, ovarian cancer, paclitaxel.

Ovarian cancer is the fifth most common cancer in women, accounting for nearly 14,000 deaths annually in the United States⁽¹⁾. Despite standard chemotherapy, nearly 70% of all ovarian cancer patients will eventually succumb to their disease. Consequently, studies have continued to investigate the activity of

novel non-cross-resistant agents in combination with standard therapy to improve the progression-free interval and overall survival in ovarian cancer patients^(2,3).

Bevacizumab (Genentech Inc., San Francisco, CA) is a recombinant humanized monoclonal antibody that binds to and, thereby, inhibits the biologic activity of human vascular endothelial growth factor (VEGF)⁽⁴⁾. The inhibition of angiogenesis through targeting the VEGF receptor ligand is a strategy that appears to be tumor specific and may be essential to the regulation of angiogenesis in epithelial ovarian carcinoma^(5,6). A

Address correspondence and reprint requests to: John P. Micha, MD, Gynecologic Oncology Associates, 351 Hospital Road, Suite 507, Newport Beach, CA 92663, USA. Email: bram@gynoncology.com

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higher degree of VEGF expression has been measured in several tumors, including lung, breast, thyroid, gastrointestinal tract, kidney, bladder, ovary, and cervix^(7,8).

Bevacizumab has been studied in several clinical trials, demonstrating promising results in patients with colorectal, lung, and breast carcinoma^(9–11). Prior studies have discussed the safety and toxicity profile of bevacizumab, reporting mild to moderate cases of hypertension, proteinuria, hemorrhage, and uncommon but manageable wound healing complications^(12,13). In particular, hypertension has been observed in several clinical trials during routine monitoring of vital signs and through reported adverse events^(6,14). Gastrointestinal (GI) perforations may also be a consequence of treatment involving bevacizumab^(15–17). Wright *et al.*⁽¹⁵⁾ reported a 9% incidence of GI perforations in their platinum-refractory ovarian cancer patients treated with bevacizumab, which raised significant safety concerns with this agent as a treatment for ovarian cancer.

Since no first-line regimen has demonstrated compelling superiority, the favorable safety profile of bevacizumab makes it an appealing addition to standard chemotherapy due to the potential synergy, distinct mechanisms of action, and opportunity to enhance treatment efficacy. We present the first completed phase II study assessing the feasibility, response rate, and toxicity of a paclitaxel, carboplatin, and bevacizumab (PCB) induction therapy regimen in advanced-stage epithelial ovarian, fallopian tube epithelial, or peritoneal carcinoma patients.

Materials and methods

Eligibility

Patients with stage III or IV primary, peritoneal, and fallopian tube adenocarcinoma were eligible for participation in this study and received initial chemotherapy within 3 weeks of cytoreductive surgery. Optimal cytoreduction was defined as tumor debulking with residual tumor less than 1 cm. An institutional review board approved the protocol and every patient signed a consent form prior to enrolment. Eligible patients had adequate bone marrow, renal, hepatic function, white-cell count of at least 3,000 per cubic milliliter, platelets of at least 100,000 per cubic milliliter, creatinine clearance greater than or equal to 50 milliliters per minute, serum bilirubin less than or equal to 1.5 times normal, serum aspartate aminotransferase less than three times normal, no previous history of chemotherapy or irradiation, and an Eastern Cooperative Oncology Group (ECOG) performance status less

than or equal to two. Study entry and initiation of chemotherapy occurred within 3 weeks of cytoreductive surgery. Exclusion criteria included septicemia, severe infection, borderline tumor diagnosis, acute hepatitis, severe GI bleeding, history of congestive heart failure, angina, or myocardial infarction within the past 6 months. Patients undergoing bowel resection surgery were eligible for inclusion.

Drug administration

Patients were treated with paclitaxel (175 mg/m²) of body surface area via 1 h infusion^(18,19) and carboplatin five times area under the curve (AUC of 5 IV) according to the Calvert formula over 30 min on day 1⁽²⁰⁾. The creatinine clearance was calculated by the method of Jelliffe⁽²¹⁾. Bevacizumab (15 mg/kg) of body weight was delivered over 90 min. Patients were initially treated with paclitaxel, followed by the carboplatin, and bevacizumab was given last. The regimen was repeated every 21 days for six cycles. Bevacizumab was not added to this chemotherapy regimen until cycle two. This was done to minimize the risk of surgical wound or bowel anastomotic healing complications. Delaying the bevacizumab until cycle two is similar to the approach used routinely for colon cancer patients following surgery. In the event of a dose delay from hematologic toxicity (eg, low absolute neutrophil count), bevacizumab was maintained on schedule.

Patients who did not achieve a complete response to induction therapy were treated at the discretion of their physician, which did not include additional therapy with bevacizumab. Granulocyte colony-stimulating factor could be initiated at the discretion of the physician. Prior to paclitaxel infusion, patients were premedicated with intravenous dexamethasone, diphenhydramine, cimetidine, ondansetron or granisetron, and lorazepam. Toxicity was graded using the National Cancer Institute criteria⁽²²⁾. Patients were required to have an absolute neutrophil count of at least 1500 per cubic milliliter, and a platelet count of at least 100,000 per cubic milliliter on day 1 to receive chemotherapy. Complete blood count values were obtained weekly until the conclusion of cycle six and then subsequently every 3 weeks.

Response evaluation

Clinical response was assessed by clinical, serologic, and radiographic means according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria⁽²³⁾. Chest x-ray and abdominal/pelvic Computed tomography (CT) scans were performed prior to initial treatment and

before cycles one and two. A complete response (CR) was defined by a normalization of CA-125 with confirmatory assessment no sooner than 28 days after the initial normal assessment⁽²⁴⁾. The CR date reflected the first CA-125 within normal limits. A partial response (PR) was determined by at least a 50% decrease from baseline in serum CA-125, but with values remaining above normal. The value showing the decrease was confirmed by an additional value no sooner than 28 days after the first value. The PR date reflected the first CA-125 with a decrease of at least 50%. In patients with normal CA-125 at baseline, progressive disease was defined as CA-125 at least two times the upper limit normal. In patients with CA-125 above the upper limit normal at baseline, progressive disease was defined as values two times the lowest value observed for that patient. Stable disease was defined as disease that does not fulfill the criteria for CR, PR, or progressive disease. After cycle six, chest x-ray and CT scans of abdomen and pelvis were repeated to determine the objective response rate. Progression-free survival was defined as the length of time from the date of entry until the date of clinical, serologic, or radiologic progression. Overall survival was defined as time from the date of entry until patient expiration, with all causes of death treated equally.

Results

From March 2005 until March 2006, twenty-one eligible stage III/IV ovarian, fallopian tube, or peritoneal cancer patients were prospectively entered into the study and received initial chemotherapy within 3 weeks of cytoreductive surgery. One patient was immediately excluded from the study prior to her first dose of bevacizumab due to disease progression. Her toxicity data was not included in the study analysis. Two patients were removed from the study prior to cycle six due to either grade 3 neuropathy or clinical deterioration (fatigue, anemia, and nutritional deficit) and were not eligible for response evaluation. One patient completed her cycle six chemotherapy and confirmatory scans but was later removed from the study because of hospitalization due to a bowel obstruction and potential for subsequent surgery. However, the patient successfully responded to conservative management with nasogastric suctioning, nothing by mouth, and total parenteral nutrition and the bowel obstruction did not recur. Patient characteristics are shown in Table 1.

Dose delivered

Out of 116 cycles, 8 (6.9%) cycles were delayed 1 week due to grade 3 or 4 neutropenia. Bevacizumab was

Table 1. Patient characteristics for trial of PCB (N = 20)

Characteristics	n (%)
Mean age (range)	58.0 (41–74)
Tumor type	
Ovarian	16 (80.0)
Peritoneal	3 (15.0)
Fallopian	1 (5.0)
Histology type	
Papillary serous	14 (70.0)
Mixed	4 (20.0)
Mucinous	1 (5.0)
Not otherwise specified	1 (5.0)
Stage	
IIIA	1 (5.0)
IIIB	1 (5.0)
IIIC	18 (90.0)
Grade	
Poor	18 (90.0)
Moderate	1 (5.0)
Well	1 (5.0)
ECOG performance status	
0	4 (20.0)
1	12 (60.0)
2	4 (20.0)
Residual disease	
Optimal	17 (85.0)
Suboptimal	3 (15.0)

associated with three dose delays due to abnormal International Normalized Ratio lab values in patients already on coumadin for a previously diagnosed deep venous thrombosis (DVT).

Response

Six patients demonstrated a CR and 10 patients exhibited a PR, resulting in a total response rate of 80%. One patient developed progressive disease and another patient exhibited stable disease. Table 2 displays the patients' tumor response rates.

Toxicity

Twenty-seven (23.3%) and 29 (25%) cycles of chemotherapy were associated with grade 3 and 4

Table 2. Trial of PCB tumor response rates (N = 18)

Response (evaluable patients) ^a	n (%)	Optimal n (%)	Suboptimal n (%)
Complete	6 (30.0)	6 (30.0)	0 (0)
Partial	10 (50.0)	9 (45.0)	1 (5.0)
Total	16 (80.0)	15 (70.0)	1 (10.0)
Progressive disease	0 (0)	1 (5.0)	0 (0)
Stable disease	0 (0)	0 (0)	1 (5.0)

^aTwo patients were not evaluated for response due to either clinical deterioration or because of grade 3 neuropathy.

neutropenia, respectively. There was no incidence of grade 3 or 4 thrombocytopenia or anemia. Two patients developed grade 3 hypertension (HTN), were subsequently managed medically by their primary-care physician, and remained on the study. There was no incidence of GI perforations. Two additional patients developed a DVT that required hospitalization, although neither case appeared to be related to the bevacizumab. The first DVT was presumably attributed to port-a-catheter placement and the second patient developed a DVT prior to receiving her first dose of bevacizumab. Their symptoms were resolved with anticoagulation therapy, and the patients continued with the study. There were no admissions for febrile neutropenia, and nonhematologic toxicity was mild and easily managed. Tables 3 and 4 illustrate the hematologic and nonhematologic toxicity patient occurrences.

Discussion

Bevacizumab is one of the first antineoplastic agents to exhibit significant activity in cancer patients by inhibiting angiogenesis or the growth of new blood vessels^(13,25). Bevacizumab appears to be a viable candidate for enhancing the efficacy of standard combination chemotherapy in ovarian cancer treatment because of its unique mechanism of action and reasonable toxicity profile⁽²⁵⁾.

Prior studies have demonstrated promising results using bevacizumab with standard therapy in regard to response rates, progression-free, and overall survival in patients with colorectal, lung, and breast carcinoma^(9–11). There have been scant studies in the field of ovarian carcinoma, albeit in recurrent disease populations^(15,26,27). Cohn *et al.*⁽²⁶⁾ examined ten patients with recurrent and refractory ovarian cancer who were treated with biweekly bevacizumab and a weekly taxane. They reported a significant, but temporary improvement in the patients' CA-125 serum levels with only mild (ie, no grade 3 or 4) toxicity observed. In a later study, 44 recurrent ovarian cancer

Table 4. Nonhematologic toxicity for trial of PCB (N = 20)

Toxicity	HTN	Neuropathy
	Number of patients (%)	
Grade 1	8 (40.0)	10 (50.0)
Grade 2	1 (5.0)	0 (0)
Grade 3	2 (10.0)	1 (5.0)
Grade 4	0 (0)	0 (0)

patients were treated with bevacizumab and examined for response and progression-free survival⁽²⁸⁾. Although a 16% objective response rate was reported, the study was closed prematurely due to an unexpected incidence of bowel perforations.

We present herein results from the first completed phase II study assessing the feasibility, response rate, and toxicity of a PCB primary induction therapy in patients with advanced-stage ovarian carcinoma. Penson *et al.*⁽²⁹⁾ reported preliminary phase II results from their first-line study involving PCB for the treatment of advanced müllerian tumors. Thirteen of the 30 patients in their study had completed chemotherapy. Acceptable toxicity was reported, including only 2.3% of cycles associated with grade 4 neutropenia and one episode of febrile neutropenia.

At the doses examined, we encountered a total response rate of 80%. This was higher than the 75% reported response rate associated with standard therapy involving paclitaxel and carboplatin^(29,30), but lower than alternate triplet regimens^(2,31,32). However, we recognize the concerns when comparing different regimens involving larger patient populations, particularly with the current phase II study. Furthermore, there may be some difficulty associated with evaluating the impact of experimental treatment to standard therapy, whose response rates have been confirmed in historical trials⁽³³⁾.

We suspect that our lower response rate may be attributed to the RECIST criteria, whose stringent and objective guidelines differ significantly from the World Health Organization criteria.

In terms of toxicity, there was a low incidence of manageable grades 3 and 4 neutropenia, with no incidence of grades 3 or 4 thrombocytopenia. Although we encountered neuropathy, the patients' activities of daily living were unaffected. In their ongoing phase II study involving PCB, Penson *et al.*⁽²⁹⁾ also reported reasonable hematologic toxicity with study withdrawal in one patient due to neuropathy.

Nonhematologic toxicities associated with bevacizumab include HTN and GI perforations^(12,13). In our study, there was a low incidence (10%) of grade 3

Table 3. Hematologic toxicity for trial of PCB (N = 20)

	Neutropenia	Thrombocytopenia	Anemia
	Number of patients (%)		
Grade 1	0 (0)	18 (90.0)	10 (50.0)
Grade 2	2 (10.0)	0 (0)	9 (45.0)
Grade 3	5 (25.0)	0 (0)	0 (0)
Grade 4	13 (65.0)	0 (0)	0 (0)

HTN, and none of the patients developed GI perforations. We anticipated a greater degree of HTN since prior studies have reported clinically relevant HTN associated with bevacizumab^(6,14). Penson *et al.*⁽²⁹⁾ similarly reported a low incidence of grade 3 HTN and, also, no bowel perforations.

We suggest that the risk of bevacizumab and associated bowel perforations is mitigated in optimally debulked patients with little or no gross residual disease on the bowel. This appears to contrast with the high incidence of bowel perforations reported in retrospective recurrent ovarian cancer patient studies involving clinical care with single agent or combination bevacizumab therapy^(15,28).

In the current study, one patient completed her cycle of six chemotherapy and confirmatory scans but was eventually hospitalized for a bowel obstruction. She responded favorably to conservative treatment, and the bowel obstruction did not recur. Two patients were hospitalized for a DVT and remained on study, but neither case appeared to be related to the bevacizumab. DVTs are common in ovarian cancer patients because they are secondary to hypercoagulability, bed rest, and indwelling venous catheters.

Currently, clinical knowledge discussing the efficacy of bevacizumab in this patient population is limited. While we cannot make any definitive conclusions regarding the efficacy of PCB from a single-arm study, our relatively high-total response rate and reasonable toxicity profile suggest that this regimen may have promise for patients with advanced-stage epithelial ovarian, fallopian tube, or peritoneal cancer. The lack of bowel perforations in our study is encouraging. When the data matures, we will be able to report on patient progression-free survival and overall survival, which may be more important in further evaluating the efficacy of this regimen. Additional investigation with PCB is warranted.

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Combination gemcitabine, platinum, and bevacizumab for the treatment of recurrent ovarian cancer

Debra L. Richardson, Floor J. Backes, Leigh G. Seamon, Vanna Zanagnolo, David M. O'Malley, David E. Cohn, Jeffrey M. Fowler, Larry J. Copeland*

Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, The Ohio State University College of Medicine, Columbus, OH, USA

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Abstract

Objective. To describe the response rate (RR), progression-free survival (PFS), and toxicity profile of combination gemcitabine, platinum, and bevacizumab (GPB) for the treatment of recurrent epithelial ovarian cancer (EOC).

Methods. A chart review of all patients with recurrent EOC who were treated with D1, D15 GPB in a 28-day cycle at a single institution was performed. Standard doses were gemcitabine 1000 mg/m², cisplatin 30 mg/m² or carboplatin AUC 3, and bevacizumab 10 mg/kg. All patients were analyzed for toxicity. RR and PFS were assessed in all patients who received at least 2 cycles of GPB.

Results. Thirty-five patients were identified, and 33 received at least 2 cycles of GPB. The majority of patients (80%) were platinum sensitive. Patients received a median of 6 cycles of GPB (range 1–24). Sixteen patients (48%) had a complete response (CR), and 10 patients (30%) had a partial response (PR), for a total RR of 78%. An additional 5 patients (15%) had stable disease, and only 2 (6%) patients had progressive disease. The median overall PFS was 12 months (95% CI 7–15), with a median follow-up time of 10 months (2–22). Two patients (6%) had bowel perforations, and both survived. Hematologic toxicities were most common, with 29% and 14% of patients experiencing grade 3 or 4 neutropenia and thrombocytopenia respectively.

Conclusions. The combination of GPB demonstrated excellent efficacy for the treatment of recurrent EOC. However, serious toxicities occurred, and the safety profile of this combination requires further study.

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Keywords: Gemcitabine; Bevacizumab; Platinum; Recurrent epithelial ovarian cancer; Bevacizumab; Bowel perforation

Introduction

Ovarian cancer is the fourth leading cause of cancer death among women in the United States [1]. Every year about 22,000 women are diagnosed with ovarian cancer and approximately 15,000 women will die from the disease [2]. Although about 75% of patients with EOC will respond to first-line chemotherapy with platinum and paclitaxel, most patients with advanced stage EOC will recur. However, there are multiple active chemotherapeutic agents for the treatment of recurrent EOC. Because of this, the treatment of recurrent EOC can persist for many years. While chemotherapy in the recurrent setting is not

curative, the goal of therapy is to improve quality of life and possibly extend quantity of life while minimizing side effects [3].

Preclinical trials demonstrate synergism between platinum agents and gemcitabine, and gemcitabine may overcome platinum resistance [4,5]. Pfisterer et al. demonstrated that gemcitabine plus carboplatin improves PFS with acceptable toxicity compared to single-agent carboplatin in a randomized phase III trial (median PFS 8.6 months versus 5.8 months) [6]. RR of 16–64% have been achieved with combination gemcitabine plus platinum [5–9].

Angiogenesis is necessary for tumor growth and progression [10]. Angiogenesis is regulated by both positive and negative factors, the most potent of which is vascular endothelial growth factor (VEGF) [11]. Multiple reports have shown that angiogenesis, as measured by microvessel density, is associated with worse survival for ovarian cancer patients [12–16].

* Corresponding author. M-210 Starling Loving Hall 320 West 10th Avenue Columbus, OH 43210, USA. Fax: +1 614 293 3078.

E-mail address: Larry.Copeland@osumc.edu (L.J. Copeland).

Bevacizumab is a recombinant monoclonal antibody against VEGF, and prevents angiogenesis in animal models [17–19]. As such, it has a different mechanism of action than traditional chemotherapeutic agents. Bevacizumab has been studied extensively in patients with a variety of tumor types, including colorectal, breast, lung, and renal carcinoma [20,21]. Bevacizumab has previously been combined with other multi-drug regimens, such as 5-fluorouracil/irinotecan/leucovorin for metastatic colon cancer with significantly improved survival [22]. The addition of bevacizumab to gemcitabine and carboplatin for the treatment of non-small cell lung cancer was shown to significantly improve PFS as well as RR [23].

Recent reports have demonstrated bevacizumab is active in patients with recurrent EOC. RR of 16–21% have been reported for single-agent bevacizumab for the treatment of persistent or recurrent EOC [24–26]. A recently published phase II trial of bevacizumab with oral cyclophosphamide demonstrated a RR of 24% in patients with recurrent EOC [27]. Wright et al. reported a RR of 35% for bevacizumab in combination with a cytotoxic agent in platinum-refractory EOC patients [28]. In addition, bevacizumab in combination with taxane chemotherapy improves symptoms in patients with refractory EOC [29]. Thus, bevacizumab is an attractive candidate to add to cytotoxic chemotherapy regimens and is currently being investigated in randomized clinical trials as first-line treatment (GOG 218 and ICON 7). The objective of this study is to describe the RR, PFS, and toxicity profile of combination GPB for the treatment of recurrent EOC.

Materials and methods

A retrospective chart review was performed of all patients who initiated treatment with combination GPB (cisplatin or carboplatin) for recurrent EOC between October 2005 (the first time this regimen was used at our institution) and July 2007 at a single institution. Follow-up continued until March 2008. Institutional review board approval was obtained. Patients were identified by reviewing chemotherapy log books. Both platinum sensitive (recurrence > 6 months after completing platinum-based chemotherapy) and platinum-resistant (recurrence < 6 months after completing platinum-based chemotherapy) patients were included. Charts were abstracted for pertinent demographic information, as well as toxicities and treatment response. All patients were included in the toxicity analysis. RR and PFS were calculated for patients who received at least 2 cycles of this combination treatment.

The standard treatment dose was gemcitabine 1000 mg/m², bevacizumab 10 mg/m², and either carboplatin area under the curve (AUC) 3 mg/ml/min or cisplatin 30 mg/m² on days 1 and 15 in a 28-day cycle. The creatinine clearance for calculation of the carboplatin dose was calculated according to the Jelliffe method. Patients were pre-medicated with ondansetron, dexamethasone, and lorazepam, and metoclopramide, dexamethasone, and ativan were given to prevent delayed emesis. The use of granulocyte-colony stimulating factors (G-CSF) and erythropoietin stimulating agents (ESAs) was per physician discretion.

Measurable disease was defined as at least one lesion that was greater than 1cm on spiral CT, as defined by Response to

Treatment in Solid Tumors (RECIST) criteria [30]. In the absence of measurable disease, CA-125 levels were used to assess response per modified Rustin criteria [31]. Complete response was disappearance of gross evidence of disease, resolution of measurable disease on CT scan, or a normalization of CA-125 levels from an elevated level. Partial response was a 30% or greater reduction in measurement of longest dimension of each lesion, or >50% decrease in CA-125 levels. Progressive disease was a 20% or greater increase in measurement of longest dimension of each lesion or the appearance of any new lesion, or a doubling of CA-125 levels within 8 weeks of the start of chemotherapy. Stable disease was any condition which did not meet the above criteria. Best response was reported. CA-125 levels were routinely drawn with the standard pre-chemotherapy labs. CT scans were obtained as appropriate to follow measurable disease and at the physician's discretion. The NCI CTCAE Version 3.0 was used to evaluate toxicities. The worst grade toxicity in each category per patient was reported. PFS is the time from the date of first treatment with combination gemcitabine, platinum, and bevacizumab until disease progression or date of last contact.

Statistical analysis

Simple descriptive statistics were used to report response rates and frequency and severity of toxicities, including percentages, 95% confidence intervals, means, and medians as appropriate. Chi-square was used to calculate differences in proportions. Overall PFS was determined using the Kaplan Meier survival curve. Stata release 10 (College Station, Texas) was used to perform statistical calculations.

Results

Thirty-five subjects were identified, and all were included in the toxicity analysis. Seventeen of these patients are part of an ongoing prospective phase II trial of gemcitabine, carboplatin, and bevacizumab for the treatment of recurrent ovarian cancer. Ninety-four percent (33/35) of the subjects received at least 2 cycles and were analyzed for RR and PFS. The median age was 60 years, and the majority of the subjects were Caucasian. Eighty percent (28/35) of the patients were primarily platinum sensitive. Of these, 21% (6/28) had developed secondary platinum resistance (Table 1).

Patients had received a median of 2 prior chemotherapy regimens (range 1–11). All patients had been treated with platinum-based first-line chemotherapy. The median platinum-free interval was 13 months (range 0–50 months). Seven patients (20%) had received combination gemcitabine and platinum previously. Bevacizumab was added to combination gemcitabine and cisplatin after 4 cycles in 1 patient, and after 5 cycles in another. Seven patients (20%) had been treated with bevacizumab in the past. No patients were treated with combination GPB prior to this study.

Of the 33 patients analyzed for response and PFS, 21 patients received carboplatin while 12 patients were treated with cisplatin combined with gemcitabine and bevacizumab. Two patients had cisplatin substituted for carboplatin due to persistent neutropenia

Table 1

Baseline demographics (N=35)	Number (%) ^a
Median age (range), years	60 (41–77)
Race	
Caucasian	30 (86)
African-American	3 (9)
Unknown	2 (6)
Stage at diagnosis	
I	3 (9)
II	4 (11)
III	25 (71)
IV	2 (6)
Not staged	1 (3)
Histology	
Serous	24 (69)
Endometrioid	3 (9)
Mixed epithelial	3 (9)
Clear cell	1 (3)
Transitional	1 (3)
Unknown	3 (9)
Grade at diagnosis	
1	2 (6)
2	3 (9)
3	28 (80)
Unknown	2 (6)
Residual disease at primary surgery	
No gross residual	13 ^b (37)
Optimal (<1 cm)	20 (57)
Suboptimal (>1 cm)	1 (3)
Unknown	1 (3)
Platinum response	
Sensitive	28 (80)
Resistant/refractory	7 (20)
Secondary resistant	6
Measurable disease	20 (61)
Median platinum-free interval (range), months	13 (0–50)
Median number of previous chemotherapeutic regimens	2 (1–11)

^a Percentages may not add up to 100% due to rounding.

^b One patient received 4 cycles of neoadjuvant chemotherapy.

in one case and thrombocytopenia in the second case. There were several deviations from the standard regimen. The carboplatin doses ranged from AUC 2.5–3, cisplatin 25–30 mg/m², gemcitabine 600–1000 mg/m², and 1 patient was treated with bevacizumab 5 mg/kg. One patient was started on a 21 day cycle (omitting day 15), and three patients were changed to gemcitabine, platinum, and bevacizumab every 21 days for recurrent cycle delays. Eleven patients had the dose of gemcitabine reduced, usually by 20%.

Patients received a median of 6 cycles of combination GPB (range 1–24). Nineteen of the 35 patients (54%) experienced treatment delays. Ten percent (4/482) of treatments were delayed for a median of 1 week (range 1–8 weeks). Treatment delay was more common for patients who received carboplatin in addition to gemcitabine and bevacizumab, as compared to patients who received cisplatin. 36% (5/14) of the patients who were treated with cisplatin were delayed, versus 74% (17/23) of the patients treated with carboplatin ($p=0.05$). The most common reason for treatment delay was thrombocytopenia (cisplatin and carboplatin), followed by neutropenia (carboplatin). Sixteen patients (46%) received G-CSF, and 22 (63%) received erythropoiesis stimulating agents.

Response data (Table 2)

Twenty patients (61%) had measurable disease, while the other 13 patients were followed with CA-125 levels only for response (Table 2). Forty-eight percent (16/33) of patients had a CR (95% CI 31 to 66%), and 30% (10/33) had a PR (95% CI 16 to 49%), for a total RR of 78% (95% CI 61 to 91%). In addition, 5 patients (15%) had stable disease, and only 2 patients (6%) had progressive disease. Ninety percent (19/21) of the patients who were platinum sensitive at the time of treatment with this combination had either a CR or PR, and none had progressive disease. Sixty-seven percent (4/6) of the patients who had developed secondary platinum resistance prior to this treatment responded, and only 1 patient progressed. Of the 6 patients who were primarily platinum-resistant/refractory and evaluable for response, there were 2 (33%) complete responders and 1 (17%) partial responder (see Table 3). Seventy percent of patients with measurable disease were responders (8 CR and 6 PR), compared to 93% of patients followed with CA-125 levels for best response (8 CR and 4 PR). Both patients with progressive disease had measurable disease.

The median overall PFS was 12 months (95% CI 7–15 months), with a median follow-up time of 15 months (range 6–26 months) (see Fig. 1). One patient was lost to follow-up after 7 cycles with stable disease. Two patients were still undergoing treatment with combination GPB at the end of this study. Ten (30%) patients had combination GPB discontinued due to complete CR. Eight patients had this treatment stopped due to progressive disease. Treatment with this combination was stopped in 14 patients due to side effects, 6 who had no evidence of disease, and 8 who had evidence of disease. At last follow-up, 10 subjects had died of disease, 19 subjects were alive with disease, and 6 subjects had no evidence of disease.

Toxicity data (Table 3)

The most common Grade 3 and 4 toxicities were hematologic. Twenty-nine percent (10/35) of subjects had Grade 3 or 4 neutropenia. Grade 3 and 4 anemia occurred in 11% (4/35) and thrombocytopenia in 14% (5/35) of subjects. Grade 3 and 4 non-hematologic toxicities were uncommon (<10%). However, 2 patients (one with no history of hypertension) developed malignant hypertension requiring hospitalization. Carboplatin was discontinued in 3 patients for hypersensitivity reactions, and cisplatin in 1 patient for a reaction. While three patients had grade

Table 2

Response data (N=33)	Number (%) ^a			
Platinum sensitivity	CR	PR	Stable	Progressive
Platinum-sensitive ^b	13 (61)	6 (29)	2 (10)	0
Secondary platinum-resistant	1 (17)	3 (50)	1 (17)	1 (17)
Platinum-resistant/refractory	2 (33)	1 (17)	2 (33)	1 (17)
Total	16 (48)	10 (30)	5 (15)	2 (6)

^a Percentages may not add to 100 due to rounding.

^b Platinum sensitive at time of treatment with gemcitabine, platinum, and bevacizumab.

3 neuropathies, 1 of these was a pre-existing grade 3 neuropathy, and 1 occurred in a patient with a pre-existing grade 2 neuropathy. In total, sixteen patients (46%) had pre-existing neuropathy from previous chemotherapy, the majority (56%) of which was grade 2.

Thirteen subjects were hospitalized for a total of 17 hospital stays during treatment with this combination therapy. Reasons for hospitalization were as follows: placement of VP shunt (unrelated to chemotherapy), anti-coagulation for deep venous thrombosis, failure to thrive, dehydration due to diarrhea, malignant hypertension, hypercalcemia secondary to bone metastases, hyponatremia, fever (no identified source), rectal bleeding, small bowel obstruction, carboplatin administration for hypersensitivity, streptococcal bacteremia, enterovaginal fistula, and bowel perforation.

There were 3 serious gastrointestinal complications. Two patients were diagnosed with bowel perforation, and 1 patient developed an enterovaginal fistula while on treatment. The first bowel perforation occurred after cycle #2 in a platinum sensitive patient who had a CR. An abdominal CT scan revealed an anastomotic leak from the site of her ileo-cecal anastomosis which was performed 15 months prior, with an associated abscess. Of note, the patient had only received one previous chemotherapy regimen. The second bowel perforation occurred after 5 cycles of triple combination chemotherapy in a platinum sensitive subject with a CR. This patient had no prior history of bowel surgery, and had received 2 previous chemotherapy regimens. She was diagnosed with a perforated diverticular

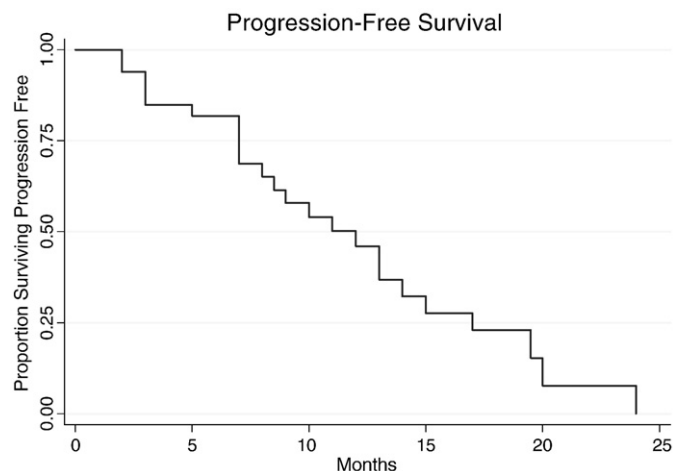


Fig. 1. Kaplan–Meier curve for time to progression. Median PFS was 12 months (95% CI 7–15), with a median follow-up time of 10 months.

abscess. The enterovaginal fistula occurred after 3 cycles of GPB in a patient with stable disease.

There was one death while on treatment with combination GPB (cisplatin). This 52 year old patient with a history of well-controlled hypertension and lupus had received 7 cycles of GPB when she was hospitalized for work-up and treatment of hypercalcemia. The patient was noted to have progressive disease, including bone metastases with spinal cord compression. She underwent a neurosurgical procedure for management of the spinal cord compression and spine stabilization, and had a massive cerebrovascular accident on post-operative day (POD) #11. After discussion with the family, the patient was changed to comfort care status and expired POD #14.

Discussion

The combination of GPB is highly active in the treatment of recurrent EOC, with a RR of 78% and a median PFS of 12 months. While single-agent bevacizumab has demonstrated modest activity (RR 16–21%) in patients with platinum-resistant/refractory disease, the addition of bevacizumab to cytotoxics has resulted in a reported RR of 35% [24–26,28]. The higher RR in this study compared to previously published studies incorporating bevacizumab may be attributable to the inclusion of platinum sensitive patients, although the CR in 2 platinum-resistant patients is noteworthy. The RR in this study compares favorably to published RR (16–64%) for combination gemcitabine and platinum, with a longer PFS in the present study [5–9]. The low rate of progressive disease is notable, as 20% of patients had received combination gemcitabine and platinum previously and 20% had been treated with bevacizumab in the past.

While the RR and duration of response are promising, significant toxicities were noted. The occurrence of bowel perforations in ovarian cancer patients treated with bevacizumab has been reported to be 0–15% [24–29,32]. In fact, a phase II trial of bevacizumab in platinum-resistant EOC patients was halted early because of a higher than expected gastrointestinal perforation rate [25]. A recent paper suggested that careful

Table 3
Toxicity data

	Patients, <i>N</i> (%)			<i>(N</i> =35)	
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Leukopenia	9 (26)	11 (31)	7 (20)	0	0
Neutropenia	5 (14)	8 (23)	8 (23)	2 (6)	0
Anemia	10 (29)	14 (40)	4 (11)	0	0
Thrombocytopenia	11 (31)	7 (20)	4 (11)	1 (3)	0
Fatigue	8 (23)	20 (57)	3 (9)	0	0
Pain	4 (11)	10 (29)	3 (9)	0	0
Headache	3 (9)	0	0	0	0
Constipation	16 (46)	2 (6)	0	0	0
Diarrhea	4 (11)	1 (3)	1 (3)	0	0
Nausea	10 (29)	6 (17)	3 (9)	0	0
Fistula, enterovaginal	0	0	1 (3)	0	0
Perforation, GI	0	0	2 (6)	0	0
Neuropathy					
Cranial	0	1 (3)	0	0	0
Sensory	7 (20)	15 (43)	3 (9)	0	0
Creatinine	1 (3)	1 (3)	0	0	0
Proteinuria	4 (11)	10 (29)	0	0	0
Hemorrhage	6 (17)	3 (9)	0	0	0
Thromboembolic	0	0	1 (3)	0	0
Hypertension	1 (3)	3 (9)	1 (3)	2 (6)	0
Liver function tests	4 (11)	1 (3)	0	0	0
Dyspnea	0	2 (6)	0	0	0
CNS ischemia	–	0	1 (3)	0	1 (3)
Allergy	1 (3)	2 (6)	3 (9)	0	0
Mucositis	4 (11)	1 (3)	0	0	0
Rash	0	1 (3)	0	0	0

patient selection may reduce the risk of bowel perforation, by avoiding bevacizumab in patients with clinical symptoms of bowel obstruction, pelvic exam consistent with rectosigmoid involvement, or bowel involvement on CT scan [33]. However, these risk factors were not present in our 2 patients who developed gastrointestinal perforation. Wright et al. suggest that bevacizumab should be incorporated earlier in treatment, as the 2 patients in their paper who suffered from bowel perforation were heavily pretreated [34]. Our patients who experienced gastrointestinal perforation were not heavily pretreated, having received 1 and 2 prior chemotherapy regimens respectively. In addition to bowel perforations, there have been 4 reported fistulas in EOC patients treated with bevacizumab. Further study is required to understand the mechanisms underlying bowel perforation and fistula formation in EOC patients treated with bevacizumab, and to determine if this complication is avoidable by patient selection.

Hematologic toxicities are common when gemcitabine and platinum are combined for the treatment of recurrent EOC. Grade 3 and 4 neutropenia ranges from 28–77% in patients treated with D1, D8 gemcitabine and platinum, depending on the usage of G-CSF support and dose of gemcitabine used [5,6,8,9,35,36]. Oxaliplatin has been combined with gemcitabine in a biweekly treatment schedule, with less hematologic toxicity [37,38]. Bozas et al. demonstrated a significant reduction in grade 3 and 4 neutropenia by using a D1, D15 regimen of combination cisplatin and gemcitabine. The rates of grade 3 and 4 hematologic toxicity in the present study are similar to those reported by Bozas et al [7]. The degree of neuropathy was not surprising, considering almost half of the patients had pre-existing neuropathy. One patient died while on treatment from an arterial thromboembolic event, possibly related to treatment, though the patient had recently undergone a neurosurgical procedure.

There are several limitations to this study. It is retrospective, and therefore subject to the inherent biases of retrospective studies, including selection bias. The treatment doses varied somewhat, but this is probably reflective of real world practice. There is no control group, so the effect that bevacizumab had on the RR cannot be directly measured. The patients were heterogeneous and included platinum sensitive and platinum-resistant patients. Because of the pre-clinical and clinical data suggesting synergism between gemcitabine and platinum, and the high response rates in platinum-resistant patients, we decided to include platinum-resistant patients [4,5,7,8].

In conclusion, combination GPB is highly efficacious in the treatment of recurrent EOC, with an overall response rate of 78%. However, serious adverse events from the addition of bevacizumab to gemcitabine and platinum occurred, especially hypertension and gastrointestinal complications. Currently, the dilemma for the clinician is when to incorporate bevacizumab in the treatment of recurrent EOC. The optimal timing of incorporation of bevacizumab in the treatment of recurrent EOC, the ideal patient, and the appropriate dose is unknown. The risk/benefit profile of the addition of bevacizumab to current cytotoxic regimens has to be carefully weighed. Further studies of the safety profile of this combination are warranted.

In addition, prospective comparisons of combination chemotherapy with and without bevacizumab (GOG 213 and the OCEANS trial) will help to better define the risk/benefit profile of the addition of bevacizumab to cytotoxic chemotherapy for recurrent EOC treatment.

Conflict of interest statement

Some of the patients included in this retrospective study are part of an ongoing prospective phase II trial at The Ohio State University. Funding is provided by Genentech, Inc and Eli Lilly, Corporation. Their funding is evenly distributed by patient enrollment. The funding is not granted until patients are enrolled onto the trial. None of the investigators have any conflicts to disclose.

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