SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RAD: 12-69261- -5 **FECHA**: 2014-01-24 11:05:48
DEP: 2020 DIRECCION DE NUEVAS CREACIONES **EVE:** 379 FASE NACIONAL INCLUIDO CAPITULO II
TRA: 11 PCT-PATENTE DE INVENCION CAPITULOS I Y II **FOLIOS**: 8
ACT: 519 PRESENTACION

DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado(a)/Señor(a)
CARLOS REINALDO OLARTE GARCIA

Asunto: Radicación: 12-69261- -5
Trámite: 11
Evento: 379
Actuación: 519
Oficio: 685
Folios: 8

Patente de Invención	**X**			Patente de Modelo de Utilidad	
Vía Nacional					
Vía PCT (Fase Nacional)	**X**	Capítulo I		Capítulo II	**X**
No. Solicitud Internacional	PCT/IB2010/054866				
Fecha de Presentación Internacional	27/10/2010				

1. Documentos estudiados

Descripción:	Radicación 12-69261-00000	27/Abril/2012
Reivindicaciones:	Radicación 12-69261-00000	27/Abril/2012
Figuras:	Radicación 12-69261-00000	27/Abril/2012
Prioridad(es):	US 61/256,160	29/Octubre/2009
	US 61/293,903	11/Enero/2010
	US 61/355,834	17/Junio/2010
	US 61/355,888	17/Junio/2010
	US 61/369,929	02/Agosto/2010
	US 61/383,933	17/Septiembre/2010
	US 61/389,969	05/Octubre/2010

2. Análisis de la Prioridad

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

3. Objeto de la invención

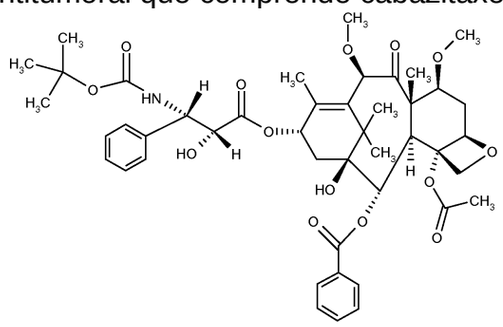
De acuerdo con lo establecido en el numeral 1.2.2.2 del Título X de la Circular Única para efectos del examen de patentabilidad, se tendrá en cuenta la tasa pagada por el solicitante al momento de comenzar el examen para las reivindicaciones

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. En el presente caso se estudiarán las reivindicaciones 1 a 33 del capítulo reivindicatorio.

Título de la solicitud: “Nuevo uso antitumoral de cabazitaxel”.

El problema planteado en esta solicitud consiste en proporcionar una opción terapéutica nueva para tratar el cáncer de próstata, especialmente en pacientes que no siguen un tratamiento basado en taxano, tales como pacientes con cáncer de próstata metastásico resistente que se han tratado previamente con un régimen basado en docetaxel.

Para resolver este problema técnico la solicitud en estudio proporciona una nueva aplicación terapéutica antitumoral que comprende cabazitaxel de fórmula:



en combinación con prednisona o prednisolona para el tratamiento del cáncer de próstata.

El objeto de la presente solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A61K31/164, A61K31/56, A61K45/06, A61P35/00.

4. Excepción a la Patentabilidad (Art 20 D 486 literal d))

La reivindicación 12 se encabeza en la forma de compuesto pero corresponde a una combinación caracterizada por referencia a elementos del método de tratamiento como es el caso de las particularidades del estadio del cáncer (cáncer de próstata metastásico), resistente a la castración (es decir no dependiente de hormonas) o en el caso de cáncer refractario a las hormonas (recidivante) que previamente se ha tratado con un régimen basado en docetaxel. Por lo anterior, se sugiere a la solicitante eliminar la reivindicación citada y sus dependientes.

Las reivindicaciones 17 a 19 se encabezan en términos de compuesto pero se caracterizan en términos del método de diagnóstico porque se refieren a la toma de muestras de sangre de pacientes que padecen cáncer con el fin de medir los niveles de neutrófilos como indicador de toxicidad de la terapia.

Las reivindicaciones 21 a 24 definen un método de tratamiento para reducir la neutropenia en un paciente con cáncer de próstata, materia que se encuentra exceptuada de patentabilidad de acuerdo con el art. 20 lit d) D 486.

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

Las reivindicaciones 32 y 33 corresponden a un método de promoción del uso de cabazitaxel en el tratamiento del cáncer por referencia a las indicaciones e instrucciones de uso. El uso no es una categoría inventiva de acuerdo con el art 14 D 486, por lo que se sugiere retirarlas del capítulo reivindicatorio.

6. De la solicitud de patente

Titulo

El título no corresponde con el objeto de la solicitud porque hace referencia al uso terapéutico. Se sugiere a la solicitante asignar un nuevo título a la solicitud indicando los elementos combinados.

Reivindicaciones (Art. 30 D 486)

La reivindicación 1 se encabeza en términos del compuesto cabazitaxel, pero se caracteriza en términos de una combinación farmacológica con un segundo compuesto como prednisona o prednisolona. Al respecto es pertinente señalar que si se trata de un único sistema de entrega farmacéutico que comprende los dos compuestos combinados la reivindicación se debe encabezar en la forma de "Composición".

Las reivindicaciones 2 a 5 se encabezan en la forma de compuesto pero se caracterizan en términos de la indicación terapéutica y las condiciones clínicas de los pacientes que deben acudir al tratamiento de cabazitaxel en combinación con prednisona o prednisolona cuando no responden a las terapias de primera línea de tratamiento indicadas. Al respecto es pertinente señalar que un compuesto solo se caracteriza por su estructura y que las ventajas, indicaciones o condiciones de los pacientes no son características de un producto, bien sea que se trate de un compuesto, una composición o un kit de partes en los términos de la combinación de agentes farmacológicos, por lo anterior, se sugiere a la solicitante retirar las indicaciones del capítulo reivindicatorio.

La reivindicación 6 se encabeza en los términos de compuesto, pero se presenta en forma dependiente de las reivindicaciones 1 a 5, en las que se está caracterizando una combinación de agentes farmacológicos. En este caso se presenta una falsa dependencia, comoquiera que se pretende caracterizar el primer compuesto (cabazitaxel) porque se encuentra en la forma de un pseudopolimorfo que incorpora dentro de su red cristalina moléculas de acetona para obtener el solvato estequiométrico: (2R,2S)-3-(terc-butoxicarbonil)amino-2-hidroxi-3-fenilpropionato de 4alfa-acetoxi-2alfa-benzoiloxi-5beta,20epoxi-1beta-hidroxi-7beta,10beta-dimetoxi-9-oxo-11-taxen-13alfailo acetona, por referencia a la combinación. Se sugiere encabezar la reivindicación en términos de la composición que incluye los agentes combinados en la que el primer componente, cabazitaxel, se presenta en la forma de un solvato de acetona. Por otra parte, se recuerda a la solicitante que el compuesto cabazitaxel por sí solo se encuentra comprendido en el estado de la técnica por lo que no se puede formular una reivindicación en los términos del compuesto porque esto equivale a solicitar la exclusividad nuevamente sobre la estructura molecular.

La reivindicación 7 se presenta en forma dependiente de la reivindicación 6, por lo que se sugiere revisar el encabezado de las reivindicaciones para solucionar las falsas dependencias.

Las reivindicaciones 8 y 9 se refieren a la dosis administrada por combinación de agentes, en este caso se sugiere a la solicitante encabezar la reivindicación en los términos de kit de partes que comprende la combinación de agentes cabazitaxel con prednisona o prednisolona en la que las dosis administradas se encuentran en el rango señalado para cada agente.

Las reivindicaciones 10 y 11 se encabezan en los términos de compuesto pero se caracterizan en la forma de las indicaciones del régimen de administración. Se sugiere a la solicitante eliminar la referencia al régimen debido a que esto corresponde a materia exceptuada de patentabilidad de acuerdo con el art. 20 literal d) D 486.

Las reivindicaciones 14 a 16 se encabezan en términos de compuesto y se definen por referencia a los parámetros farmacocinéticos como área bajo la curva (AUC), concentración máxima (Cmax) y depuración renal (Aclaramiento plasmático). Al respecto es pertinente señalar que las ventajas farmacocinéticas no son características de la combinación sino resultados que se pretenden alcanzar por lo que se sugiere retirarlas del capítulo reivindicatorio.

La reivindicación 20 de composición debe incluir la caracterización de los elementos combinados, es decir, tanto al compuesto cabazitaxel como al segundo compuesto prednisona o prednisolona.

Las reivindicaciones 25 y 26 caracterizan un artículo de fabricación. Al respecto es pertinente señalar que si se trata del kit de partes éste se debe definir en términos de las preparaciones combinadas, la potencia etiquetada de cada ingrediente activo y de ser el caso sus excipientes, y no en los términos del material de envasado, la etiqueta o inserto porque estos elementos corresponden a las indicaciones del método de tratamiento, por lo anterior, se sugiere retirarlas del capítulo reivindicatorio.

7. Unidad de invención (Art 25 D 486)

El capítulo reivindicatorio presenta dos grupos de invenciones que no comparten elementos técnicos particulares:

Grupo Inventivo 1. Combinaciones de cabazitaxel con prednisona/prednisolona y composiciones que la comprenden (reivindicaciones 1 y 20)

Grupo Inventivo 2. Envase que comprende cabazitaxel y sus instrucciones de administración (reivindicaciones 27 a 31).

Los envases corresponden a un sector técnico diferente y no se pueden caracterizar en términos de su contenido. Por otra parte, no se encuentra el sustento correspondiente al diseño de un nuevo envase por la estructura o disposición de los materiales.

8. Determinación del Estado de la Técnica

El estado de la técnica se determinó con base en la fecha de presentación internacional: octubre 29 de 2009 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud.

Ítem	Documento	Título	Fecha de Publicación
D1	Mita Alain C. et. al.	"Phase I and Pharmacokinetic Study of XRP6258 (RPR116258A), a Novel Taxane, administered as a 1-hour infusión every 3 weeks in patients with advanced solid tumors"	15/Enero/2009
D2	Tannock Ian F. et al.	"Docetaxel plus predinsone or mitoxantrone plus mitoxantrone plus prednisone for advanced prostate cáncer"	7/Octubre/2004
D3	US2005065138	"Acetone solvate of dimethoxy docetaxel and its process of preparation"	24/Marzo/2005

El documento D1 divulga un estudio clínico fase I para la determinación de la máxima dosis tolerada del compuesto cabazitaxel (XRP6258) realizado sobre 25 pacientes con tumores sólidos avanzados en cuatro niveles de dosificación (10 a 25mg/m^2) administrado en infusión vía IV cada 3 semanas (Pág. 724, Col. 2).

El documento D2 divulga un estudio clínico fase III aleatorizado y multicentrico para la evaluación de la eficacia de la combinación docetaxel + prednisona en comparación con mitoxantrona + prednisona, realizado en pacientes con cáncer prostático avanzado refractario a hormonas divididos en 3 brazos: (i) docetaxel 75mg/m2 IV infusión 1h el día 1 cada 21 días + prednisona 5mg VO dos veces al día desde el día 1, (ii) docetaxel 30mg/m2 IV infusión 0,5h los días 1, 8, 15, 22 y 29 en un ciclo de 6 semanas + prednisona 5mg VO dos veces al día desde el día 1, (ii) mitoxantrona 12mg/m2 IV infusión 0.5h el día 1 cada 21 días + prednisona 5mg VO dos veces al día desde el día 1 (Pág. 1503, Col. 2 a Pág. 1504, Col. 2). El estudio evidencia que la combinación de docetaxel cada 21 días + prednisona disminuye la razón de riesgo de muerte (0.76), PSA, dolor y mejoramiento de la calidad de vida frente al grupo de mitoxantrona + prednisona (Pág. 1507, Col. 2 a Pág. 1509, Col. 1).

El documento D3[1] divulga el solvato acetona de (2R,2S)-3-(terc-butoxicarbonil)amino-2-hidroxi-3-fenilpropionato de 4alfa-acetoxi-2alfa-benzoiloxi-5beta,20epoxi-1beta-hidroxi-7beta,10beta-dimetoxi-9-oxo-11-taxen-13alfailo y el proceso para la obtención del mismo que comprende cristalizar el compuesto cabazitaxel en una mezcla de agua/acetona; donde dicho solvato contiene en promedio 7% en peso de acetona (Pág. 1, Párr. [0010-0021]).

Examen de Patentabilidad (Art 14 D486)
Novedad (Art 16 D 486)

La reivindicación 6 consiste en el compuesto cabazitaxel en la forma de un solvato

1 http://worldwide.espacenet.com/publicationDetails/biblio?DB=worldwide.espacenet.com&II=0&ND=3&adjacent=true&locale=en_EP&FT=D&date=20050324&CC=US&NR=2005065138A1&KC=A1

de acetona que contiene entre 5 y 8% en peso de acetona.

Características esenciales	D3
el compuesto cabazitaxel en la forma de un solvato de acetona que contiene entre 5 y 8% en peso de acetona.	solvato acetona de (2R,2S)-3-(terc-butoxicarbonil)amino-2-hidroxi-3-fenilpropionato de 4alfa-acetoxi-2alfa-benzoiloxi-5beta,20epoxi-1beta-hidroxi-7beta,10beta-dimetoxi-9-oxo-11-taxen-13alfailo que contiene en promedio 7% en peso de acetona (Pág. 1, Párr. [0010-0021]). .

En conclusión, las características esenciales de la reivindicación 6 se encuentran anticipadas por D3 que divulga el solvato acetona de (2R,2S)-3-(terc-butoxicarbonil)amino-2-hidroxi-3-fenilpropionato de 4alfa-acetoxi-2alfa-benzoiloxi-5beta,20epoxi-1beta-hidroxi-7beta,10beta-dimetoxi-9-oxo-11-taxen-13alfailo y el proceso para la obtención del mismo que comprende cristalizar el compuesto, donde dicho solvato contiene en promedio 7% en peso de acetona (Pág. 1, Párr. [0010-0021]).

En consecuencia, la reivindicación 6 no es nueva, según lo divulgado en el documento D3.

Por su parte, las reivindicaciones dependientes 7 a 9 no mencionan elementos esenciales adicionales que hagan nuevo el compuesto de la reivindicación 6, por lo cual se considera que tampoco cumplen con el citado requisito.

Nivel Inventivo (Art 18 D 486)

La reivindicación 1 consiste en una combinación que comprende cabazitaxel que puede estar en forma de base o en forma de hidrato o en forma de solvato y prednisona o prednisolona (Rad. No. 12-69261-00000 de 27/Abril/2012).

Características esenciales	D2	D1
Una combinación que comprende:	una combinación que comprende:	Una composición farmacéutica que comprende:
cabazitaxel que puede estar en forma de base o en forma de hidrato o en forma de solvato	docetaxel 75mg/m2 IV infusión 1h el día 1 cada 21 días	cabazitaxel (XRP6258) (10 a 25mg/m2) administrado en infusión vía IV cada 3 semanas (Pág. 724, Col. 2).
prednisona o prednisolona	prednisona o prednisolona 5mg VO dos veces al día desde el día 1	

El documento D2 se considera el estado de la técnica cercano a la invención definida en la reivindicación 1 porque el documento D2 divulga un estudio clínico fase III realizado en pacientes con cáncer prostático avanzado refractario a hormonas divididos en 3 brazos: (i) docetaxel 75mg/m2 IV infusión 1h el día 1 cada 21 días + prednisona o prednisolona 5mg VO dos veces al día desde el día 1, (ii) docetaxel 30mg/m2 IV infusión 0,5h los días 1, 8, 15, 22 y 29 en un ciclo de 6 semanas + prednisona 5mg VO dos veces al día desde el día 1, (ii) mitoxantrona 12mg/m2 IV infusión 0.5h el día 1 cada 21 días + prednisona 5mg VO dos veces al día desde el día 1 (Pág. 1503, Col. 2 a Pág. 1504, Col. 2). El estudio evidencia que la combinación de docetaxel cada 21 días + prednisona disminuye la razón de riesgo de muerte (0.76), PSA, dolor y mejoramiento de la calidad de vida frente al grupo de

mitoxantrona + prednisona (Pág. 1507, Col. 2 a Pág. 1509, Col. 1).

Por su parte, el documento D1 divulga un estudio clínico fase I para la determinación de la máxima dosis tolerada del compuesto cabazitaxel (XRP6258) realizado sobre 25 pacientes con tumores sólidos avanzados en cuatro niveles de dosificación (10 a 25mg/m^2) administrado en infusión vía IV cada 3 semanas (Pág. 724, Col. 2).

Las diferencias entre la invención, definida en la reivindicación 1 y la combinación divulgada en el documento D2 consiste en que D2 no incorpora cabazitaxel en la combinación.

Las diferencias entre la invención, definida en la reivindicación 1 y la composición divulgada en el documento D1 consiste en que D1 no enseña la combinación de cabazitaxel con prednisona o prednisolona.

El efecto que se logra por el hecho de combinar cabazitaxel y prednisona o prednisolona es obtener una nueva opción terapéutica para tratar el cáncer de próstata.

Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular así: cómo modificar la combinación de un taxano y prednisona/prednisolona divulgada en D2 modificando el docetaxel por su equivalente terapéutico cabazitaxel divulgado en D1 para obtener una una opción terapéutica nueva para tratar el cáncer de próstata.

En consecuencia, la persona del oficio normalmente versada contaba con la sugerencia o motivación razonable para modificar la combinación de docetaxel (75mg/m^2 o 30mg/ m^2) + prednisona o prednisolona divulgada en D2, modificando el agente docetaxel por el cabazataxel (un derivado del docetaxel) con actividad en cáncer metastásico de próstata, tal como lo divulga D1, por lo cual la materia reclamada se considera obvia.

En conclusión, la reivindicación 1 no cumple con el requisito de nivel inventivo (Art. 18) y puesto que las reivindicaciones 2 a 5 no reivindican elementos esenciales que la hagan inventiva, dichas reivindicaciones tampoco cumplen con el citado requisito.

9. Conclusión

Los requisitos de patentabilidad de la presente solicitud están afectados así:

Ítem	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	Mita Alain C. et. al.	1 a 5	Nivel inventivo
D2	Tannock Ian F. et al.	1 a 5	Nivel inventivo
D3	US2005065138	6 a 9	Novedad

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 2014-01-28

Elaboró: John Fredy Hernandez MontaÑo
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Phase I and Pharmacokinetic Study of XRP6258 (RPR 116258A), a Novel Taxane, Administered as a 1-Hour Infusion Every 3 Weeks in Patients with Advanced Solid Tumors

Alain C. Mita, Louis J. Denis, Eric K. Rowinsky, et al.

Clin Cancer Res 2009;15:723-730.

Phase I and Pharmacokinetic Study of XRP6258 (RPR 116258A), a Novel Taxane, Administered as a 1-Hour Infusion Every 3 Weeks in Patients with Advanced Solid Tumors

Alain C. Mita,[1] Louis J. Denis,[1] Eric K. Rowinsky,[1] Johann S. DeBono,[1] Andrew D. Goetz,[1] Leonel Ochoa,[1] Bahram Forouzesh,[1] Muralidhar Beeram,[1] Amita Patnaik,[1] Kathleen Molpus,[1] Dorothée Semiond,[2] Michèle Besenval,[2] and Anthony W. Tolcher[1]

Abstract

Purpose: To assess the feasibility of administering XRP6258, a new taxane with a low affinity for the multidrug resistance 1 protein, as a 1-hour i.v. infusion every 3 weeks. The study also sought to determine the maximum tolerated dose and the recommended dose, to describe the pharmacokinetic (PK) behavior of the compound, and to seek preliminary evidence of anticancer activity.

Experimental Design: Twenty-five patients with advanced solid malignancies were treated with 102 courses of XRP6258 at four dose levels ranging from 10 to 25 mg/m^2. Dose escalation was based on the occurrence of dose-limiting toxicity (DLT) at each dose level, provided that PK variables were favorable. The maximum tolerated dose was defined as the dose at which at least two patients developed a DLT at the first course.

Results: Neutropenia was the principal DLT, with one patient experiencing febrile neutropenia and two others showing prolonged grade 4 neutropenia at the 25 mg/m^2 dose level. Nonhematologic toxicities, including nausea, vomiting, diarrhea, neurotoxicity, and fatigue, were generally mild to moderate in severity. XRP6258 exhibited dose-proportional PK, a triphasic elimination profile, a long terminal half-life (77.3 hours), a high clearance (mean CL, 53.5 L/h), and a large volume of distribution (mean V_{ss}, 2,034 L/m^2). Objective antitumor activity included partial responses in two patients with metastatic prostate carcinoma, one unconfirmed partial response, and two minor responses.

Conclusion: The recommended phase II dose of XRP6258 on this schedule is 20 mg/m^2. The general tolerability and encouraging antitumor activity in taxane-refractory patients warrant further evaluations of XRP6258.

The taxanes have emerged as a major class of chemotherapy agents over the last 2 decades as shown by their extensive use as single agents and in multiagent regimens to treat a wide variety of solid malignancies (1, 2). However, one potential limitation of the taxanes is their high substrate affinity for the multidrug resistance (MDR) proteins, which confer both constitutive and acquired resistance (3, 4). For this reason, efforts have been made to synthesize new taxanes that are not avid substrates for MDR proteins to ultimately broaden their antitumor spectra. The new taxane XRP6258 was selected for clinical development due to its poor affinity for the ATP-dependent drug efflux pump, P-glycoprotein 1 (ATP-binding cassette, subfamily B, member 1 encoded by the *ABCB1* gene and referred to hereinafter as P-gp), and its greater penetration of the blood-brain barrier compared with docetaxel and paclitaxel (5). XRP6258 (formula $C_{45}H_{57}NO_{14}$) is partially synthesized as a single diastereoisomer from 10-deacetyl baccatin III, the major natural taxoid derived from the needles of various *Taxus* species. XRP6258 promotes the assembly of tubulin and stabilizes microtubules against cold-induced depolymerization *in vitro* as potently as docetaxel (5).

The cytotoxicity of XRP6258 was compared with docetaxel in several murine and human cell lines (5). In docetaxel-sensitive cell lines, including P388 (murine leukemia), HL60 (human leukemia) KB (human epidermoid carcinoma), and Calc18 (human breast carcinoma), XRP6258 showed potent antitumor activity comparable with docetaxel, with 50% tumor inhibitory concentrations (IC_{50}) ranging from 0.003 to 0.029 μmol/L. However, XRP6258 was more potent than docetaxel in a broad array of cancer cell lines with acquired resistance to docetaxel due to P-gp overexpression, including P388/DOX, P388/TXT, P388/VCR, HL60/TAX, Calc18/TXT, and KBV1 (5). Resistance

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Note: Previously presented at the 37th Annual Meeting of the American Society of Clinical Oncology, May 12-15, 2001, San Francisco, California.

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Translational Relevance

The selective action of conventional cytotoxic agents depends on the relative sensitivity of proliferating tumor over critical normal cells to the effects of exposure to these drugs. One factor limiting the clinical utility of such compounds is the innate or acquired drug resistance of the tumor. Resistance may be mediated by tumor cell overexpression of efflux pumps, such as the ATP-binding cassette, subfamily B, member 1 (MDR1). Although the development of rationally targeted highly specific biological agents represents an exciting new approach to anticancer drug discovery, it is anticipated that there will be a continuing requirement to include broadly active cytotoxic agents in treatment strategies. The complementary approach of improving on the spectrum of activity or tolerability of such cytotoxic compounds therefore remains as an important therapeutic objective. The novel taxoid, XRP6258, was selected for clinical development based on encouraging cytotoxic antitumor activity in cancer cell lines expressing a multidrug resistance phenotype. This agent also showed effective penetration of the blood-brain barrier. The current phase I study was designed primarily to determine the maximum tolerated dose and the dose-limiting toxicity of XRP6258 given as a 1-hour i.v. infusion. As such, this analysis is of direct and immediate clinical relevance.

factor ratios ranged from 1.8 to 10 for XRP6258, whereas comparable values were 4.8 to 50.7 for docetaxel. Furthermore, XRP6258 showed greater cytotoxicity compared with docetaxel in a CaCo-2 human colon adenocarcinoma cell line, which exhibits primary resistance to the taxanes, due to MDR (6).

XRP6258 has also shown a broad spectrum of antitumor activity in mice bearing s.c. implanted human xenografts. For example, a high complete regression rate was observed in eight of nine human tumor cell lines evaluated in human tumor xenograft models, with long-term survivors observed in hosts bearing HCT116 colon, A549 lung, MIA PaCa-2 pancreatic, SR475 squamous cell, and Du-145 prostate cancers (5). Prominent antitumor activity was also documented in SF295 and U251 glioblastoma orthotopic models. XRP6258 retained activity against docetaxel-resistant P-gp–expressing B16/TXT melanoma xenograft models, but not against Calc18/TXT and P388/VCR, which express higher levels of *ABCB1* mRNA. Interestingly, XRP6258 was found to penetrate the blood-brain barrier, which may be due to its low affinity for the P-gp (7), and studies in mice have shown that P-gp–mediated transport at this barrier can be saturated at circulating concentrations of the drug that are likely to be therapeutically useful (8). Schedule-dependent antitumor activity and toxicity was suggested by the results of preclinical studies. Both toxicity and antitumor activity profiles seemed optimal on an intermittent day 1 and 5 dosing schedule compared with daily × 5 or split (three times daily for 5 days) dosing (5).

The encouraging spectrum of antitumor activity of XRP6258 in experimental tumor models, particularly its notable activity against docetaxel-resistant, P-gp–expressing malignancies, served as a rationale to clinical evaluations. The principal objectives of this phase I and pharmacokinetic (PK) study of XRP6258 administered as a 1-hour i.v. infusion every 3 weeks in patients with advanced solid malignancies were to (*a*) characterize the toxicities of XRP6258 administered without premedication on this schedule, (*b*) determine the maximum tolerated dose (MTD) and the recommended dose for phase II studies, (*c*) characterize the PK profile of the compound and its metabolic species, and (*d*) document preliminary evidence of antitumor activity.

Materials and Methods

Eligibility. Patients with histologically documented advanced solid malignancies refractory to conventional treatment were candidates for this study. Only patients who had received less than two prior chemotherapy regimens for metastatic disease and/or radiotherapy affecting <25% of their hematopoietic reserve were eligible. Patients who had been treated with intensive chemotherapy involving autologous stem cell rescue were not eligible. Prior anticancer therapy had to be completed at least 28 d before study enrollment (42 d for nitrosoureas and mitomycin C). Other eligibility criteria included the following: age ≥18 y; a life expectancy ≥12 wk; an Eastern Cooperative Oncology Group performance status of 0 to 2; recovery from the toxic effects of prior treatment to grade ≤1, except for alopecia; adequate organ function, including hematopoietic [absolute neutrophil count (ANC) >2.0 × 10^9/L; platelets >100 × 10^9/L], renal (creatinine <1.5 mg/dL), and hepatic (total bilirubin within normal limits, transaminases, and alkaline phosphatase ≤2.5 times the upper normal limits) functions; and a normal neurologic examination. Prior therapy with taxanes was permitted. Patients with brain metastasis, coexisting medical problems of sufficient severity to limit compliance with the study, as well as patients with a prior history of severe hypersensitivity to docetaxel or paclitaxel were considered ineligible for this study. Routine use of corticosteroids or erythrocyte-stimulating factors as well as prophylactic use of colony-stimulating factors were not permitted. Pregnant or lactating women were not eligible for this trial. Before entering the study, patients gave written informed consent according to federal and institutional guidelines.

Drug administration. XRP6258 was supplied by Sanofi aventis in single-dose vials containing 94.4 mg of active product in 2.36 mL of polysorbate 80 at the concentration of 40 mg/mL XRP6258. The XRP6258 solvent vial contained 7.33 mL of a solution of 95% ethyl alcohol/water (13/87, w/w). XRP6258 was administered as 1-h i.v. infusion every 3 wk using a polyvinyl chloride–free infusion bag and administration set. No prophylactic treatment to prevent hypersensitivity reaction or emesis was administered during the first course. These treatments were provided for subsequent courses, if clinically indicated. Corticosteroids were not permitted as prophylactic treatment for nausea and/or vomiting.

Dose escalation. The starting dose was 10 mg/m^2, which corresponds to approximately one tenth of the severe toxic dose (STD_{10}) in mice and to the single highest nonseverely toxic dose in dogs, with subsequent incremental increase to 15, 20, and 25 mg/m^2 dose levels. A minimum of three patients was treated at each dose level, and a 2-wk interval was required at each dose level from the treatment of the first patient until treatment of subsequent patients. PK variables were monitored during the first course in each patient and dose escalation was to be stopped if total area under the concentration versus time curve (AUC) for plasma was ≥10.8 μg.h/mL (a level that would have exposed the patient to concentrations corresponding to severe toxic effect level in mice). If one of three patients exhibited a dose-limiting toxicity (DLT) during the first course, three more patients were to be treated at this dose level and dose escalation was considered only if no further DLTs occurred in this group. If two or three of the first three treated patients at a dose level experienced DLT during the first course, the MTD had been reached and no further escalation was to be considered. If none of three patients exhibited a DLT, then dose

escalation could be considered without including additional patients. DLT was defined as either grade 4 neutropenia lasting longer than 5 d or associated with fever (>38.5°C); platelets <25,000/mL; or any grade 3 to 4 nonhematologic toxicity excluding nausea, vomiting, hypersensitivity reactions, or alopecia. No intrapatient dose escalation was permitted. Due to the anticipated distribution in tissues and lipophilicity of the drug, the body surface area (BSA) for dose calculation was capped at 2.1 m^2. Treatment cycles were every 3 wk. Before retreatment, patients were required to have recovered from any toxic to no more than a grade 1 severity level, and platelets, total bilirubin, and creatinine values had to meet initial protocol eligibility requirements. If recovery did not occur within 35 d from the administration of XRP6258, the patient was withdrawn from the study. Dose reduction to the previous lower dose level was to be made only in the case of DLT.

The MTD was defined as the dose at which at least two of six patients experienced DLT during the first course. The recommended dose for phase II studies was defined as one dose level below the MTD. Initially, both heavily pretreated (HP) and minimally pretreated (MP) patients were to be accrued together at the same dose level. If hematologic DLT was consistently and preferentially observed in HP patients, then the accrual to the study was to diverge into HP and MP patients to define the principal phase I end points, and the MTD was to be defined for each group. HP patients were defined as patients who had received more than six courses of an alkylating agent (except low-dose cisplatin), more than four courses of carboplatin-containing chemotherapy regimens, or greater than two courses of nitrosoureas or mitomycin C.

Pretreatment and follow-up studies. History and physical examination (including a detailed neurologic examination) were done before study entry and repeated before each course. Pretreatment evaluation included complete blood cell count, full chemistry profile, including electrolytes, transaminases, alkaline phosphatase, and total bilirubin, and electrocardiogram and urine analysis. Thereafter, complete blood cell counts were done twice a week, electrocardiogram and urine analysis were repeated before each course, and the other laboratory screens were repeated weekly. Pretreatment studies also included a routine chest radiograph and relevant radiologic studies to evaluate all sites of disease and these studies were repeated every other course. Toxicities were evaluated according to the National Cancer Institute common toxicity criteria version 1.0. Tumor responses were assessed by standard WHO response criteria.

Plasma sampling and assay. To evaluate the PK variables of XRP6258, blood samples (3 mL) were collected immediately before infusion (time 0), 30 min after the beginning of infusion, 5 min before the end of infusion, and then 5, 15, 30, and 60 min and 2, 4, 6, 10, 24, and 48 h after completion of infusion in patients treated at 10 and 15 mg/m^2. In the subsequent cohorts, patients were sampled up to 120 h (at 25 mg/m^2) and 240 h (at 20 mg/m^2) after infusion. Blood specimens were collected in heparinized tubes (lithium heparinate). The blood samples were centrifuged within 30 min at 3,000 rpm × 15 min, and the plasma was removed and placed into polypropylene tubes, labeled, frozen, and stored at -20°C until analysis. No more than 1 h was allowed between blood collection and plasma sample freezing to avoid degradation of XRP6258.

Drug concentrations of XRP6258 were measured in plasma using a validated liquid chromatography-tandem mass spectrometry method. The quantitative determination was done with RPR 109881 as an internal standard. The limit of quantitation was 1 μg/L for a 200 μL sample size. The assay accuracy, defined as the percent difference between the nominal and the mean measured concentrations of quality controls, ranged from 0.01% to 4.6% (n = 67) XRP6258 in plasma over the analysis period. The accuracy of the dilution controls (1:2 or 1:4) was 1.2% (n = 23). The precision of the assay, established by the coefficients of variation (CV) of the quality controls, ranged from 9.5% to 12% for XRP6258 in plasma over the analysis period.

PK and pharmacodynamic analyses. The PK analyses were done using WinNonlin software, version 2.1 (Scientific Consulting, Inc.). Pertinent PK variables were calculated using a three-compartment open model with a first-order elimination rate, which best fits the data. A weighting factor of $1/\hat{y}^2$ was applied to the concentration data. AUC from 0 to infinity ($AUC_{0-\infty}$), half-life of the first, second, and third phases ($t_{1/2\lambda1}$, $t_{1/2\lambda2}$, and $t_{1/2\lambda3}$, respectively, where $t_{1/2\lambda3}$ was considered the elimination half-life), total body clearance (CL), and volume of distribution at steady state (V_{ss}) were determined by modeling. The plasma concentration measured 5 min before the end of infusion (C_{max} observed) was reported and a noncompartmental analysis (trapezoidal method) was also used to estimate the AUC from 0 to 48 h [$AUC_{(0\text{-}48\ h)}$] to compare the exposure over the whole dose range. The dose proportionality of the exposure was assessed on $AUC_{(0\text{-}48\ h)}$ data after dose normalization using the Proc GLM procedure of SAS (SAS Institute) software version 8.2 followed by a test of linearity applied on $AUC_{(0\text{-}48\ h)}$ against the dose expressed in mg/m^2. The interpatient and intrapatient variability of $AUC_{(0\text{-}48\ h)}$ was estimated using the Proc MIXED procedure of SAS after normalization to the dose and log transformation with patient taken as random effect and course of treatment as fixed effect. In addition, as the drug dosing is based on BSA, the relationship between the total plasma clearance expressed in L/h and the BSA was investigated using a Proc REG procedure of SAS software. All test results with $P < 0.05$ were considered statistically significant. The relative reduction in variability was calculated according to the formula [CV for CL (L/h) - CV for CL (L/h/m^2)]/[CV for CL (L/h)] × 100 and was considered to reach statistical significance when 15 (9).

The relationships between the C_{max} and $AUC_{(0\text{-}48\ h)}$ values and hematologic effect were described using the sigmoidal maximal effect model (E_{max}), which was fitted to the data by nonlinear least-square regression (9). The coefficient of determination (R^2), the SEs for the estimated variables, and visual inspection of the fitted plots were used to gauge goodness of fit of this pharmacodynamic model.

Table 1. Patient characteristics

Characteristic	No. patients
Total patients (evaluable)	25 (25)
Sex: male/female	17/8
Age, median (range), y	60 (32-80)
ECOG performance status	
Median	1
0	12
1	12
2	1
Race	
Caucasian	18 (72%)
Oriental	1 (4%)
Hispanic	6 (24%)
Previous therapy	
Chemotherapy	22 (88%)
Prior taxane-based therapy	8 (32%)
Radiotherapy	12 (48%)
Immunotherapy	2 (8%)
Hormonal therapy	8 (32%)
Tumor type	
Prostate	8
Colon	6
Rectum	2
Unknown primary	2
Other*	7
Median number of courses/patient (range)	4 (1-9)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
*Includes one of each of the following: head and neck squamous cell carcinoma, malignant melanoma, non–small cell lung cancer, osteosarcoma, pancreatic carcinoma, renal cell carcinoma, and urothelial carcinoma.

Table 2. Dose-escalation scheme

XRP6258 dose level (mg/m^2)	New patients at this dose level (courses)	Patients reduced to this dose level (courses)	Total patients (courses)	New patients with DLT
10	3 (10)	0	3 (10)	0
15	6 (24)	1 (1)	7 (25)	1
20	9 (29)	4 (19)	13 (48)	0
25	7 (19)	0 (0)	7 (19)	3

Results

General. Between June 1, 1999 and July 12, 2001, 25 patients were treated with 102 courses of XRP6258 across four dose levels. The pertinent demographics of the patients are presented in Table 1. The median number of courses administered per patient was 4 (range, 1-9). All 25 patients (100%) were evaluable for safety and 24 patients (96%) were evaluable for efficacy. One patient treated at the 15 mg/m^2 dose level was found to be ineligible for dose level determination due to an elevated alkaline phosphatase value; the patient's toxicities are reported. Twenty-two (88%) patients had previously received chemotherapy, with eight patients having received prior taxane-based therapy. According to the criteria defined in this study, 16 and 9 patients were considered MP and HP, respectively. The numbers of patients treated at each dose, as well as the number of patients experiencing DLT at each dose level, are depicted in Table 2. Dose reduction due to hematologic toxicity was done in four patients; one patient required two dose reductions. The initiation of eight (8%) courses involving four patients were delayed due to unresolved nonhematologic toxicities, specifically fatigue and fever in two patients, or at the patient's request (two patients).

Because drug-related toxicities that exceeded grade 1 were not encountered at the first dose level, dose escalation proceeded to 15 mg/m^2. At this dose level, one patient experienced grade 3 diarrhea during course 1, and the cohort was expanded to a total of six patients, with no additional DLT. At the next higher dose level, 20 mg/m^2, DLT was not observed in the initial three patients enrolled. However, three of seven subjects experienced DLT, including febrile neutropenia in one MP patient and protracted (>5 days) grade 4 neutropenia in two HP patients at 25 mg/m^2. Therefore, the rate of DLT exceeded the predefined limits of tolerability at the 25 mg/m^2 dose level, and because no DLT was observed in six additional MP and HP patients treated at the previous dose level, 20 mg/m^2, it was considered the recommended phase II dose for both MP and HP patients.

Hematologic toxicity. The effects of XRP6258 on ANCs and platelets, as well as toxicity grade, as a function of dose level are shown in Table 3. Neutropenia was the principal toxicity encountered with XRP6258. Severe neutropenia was noted only at the 25 mg/m^2 dose level, with grade 4 events occurring in 8 of 19 (42%) evaluable courses, including the three aforementioned DLTs. The median time to ANC nadir was 12 days (range, 4-17 days). Because ANC recovery to a grade $\leq$1 occurred in all patients by day 22 ($\pm$3 days), treatment delays for unresolved hematologic toxicity were not necessary. The rate of severe toxicities did not seem greater in HP patients compared with MP patients. Neither granulocyte colony-stimulating factor (G-CSF) nor granulocyte macrophage colony-stimulating factor (GM-CSF) was given as prophylactic treatments. Four patients received G-CSF/GM-CSF support during a total of five courses following the occurrence of grade 4 neutropenia (as DLTs in two patients, at cycle 1 and cycles 1 and 2, and at cycle 5 in two others). Thrombocytopenia occurred in only two patients (two courses, one grade 3 in course 5 and one grade 1 in course 1). Except for a single episode of grade 3 anemic relevant, effects on RBCs were either mild or moderate in severity.

Nonhematologic toxicities. The most common nonhematologic toxicities are summarized in Table 4. The most common nonhematologic toxicities were gastrointestinal in nature, principally consisting of diarrhea (52% of patients), nausea (40% of patients), and vomiting (16% of patients). These toxicities were generally grade 1 to 2 in severity, except for a single patient who experienced grade 3 diarrhea in the first course at 15 mg/m^2. The event was short-lived and loperamide was administered for symptomatic management. At the 20 and

Table 3. Hematologic toxicity

Dose level (mg/m^2)	No. evaluable courses	No. courses (first course) with toxicity						
		Neutropenia					Thrombocytopenia	
		Median nadir ANC (range; μL)*	Grade 1-2	Grade 3	Grade 4	Grade 4 >5 d	Grade 3-4 + fever	PLTs (/μL) 25,000-50,000	PLTs (/μL) <25,000
10	10	4,760 (2,980-7,790)	0	0	0	0	0	0	0
15	25	2,480 (880-8,500)	9 (3)	0	0	0	0	0	0
20	48	2,280 (260-4,270)	6 (3)	0 (0)	0	0	0	0	0
25	19	990 (30-5,090)	15 (3)	4 (1)	8 (3)	2 (2)	1 (1)	1 (0)	0

Abbreviation: PLTs, platelets.
*Median values (ranges) for first course.

Table 4. Nonhematologic toxicity occurring at any grade in three or more patients (>10%)

Adverse event, no. patients (cycles)	Dose level (mg/m²)										
	10 (3 patients, 10 cycles)		15 (6 patients, 25 cycles)		20 (9 patients, 48 cycles)		25 (7 patients, 19 cycles)		All (25 patients, 102 cycles)		
	Grade 1-2	Grade 3	Grade 1-2	Grade 3	Grade 1-2	Grade 3	Grade 1-2	Grade 3	Grade 1-2	Grade 3	All
Diarrhea	1 (1)	—	4 (7)	1 (1)	4 (13)	—	4 (7)	—	13 (28)	1 (1)	14 = 56% (29 = 28%)
Fatigue	1 (5)	—	1 (4)	—	3 (15)	—	4 (5)	—	9 (29)	—	9 = 36% (29 = 28%)
Nausea	1 (2)	—	1 (1)	—	3 (13)	—	5 (3)	—	10 (19)	—	10 = 40% (19 = 19%)
Neuropathy (sensory)	1 (1)	—	1 (6)	—	3 (8)	—	4 (4)	—	9 (19)	—	9 = 36% (19 = 19%)
Vomiting	1 (1)	—	—	—	2 (8)	—	1 (1)	—	4 (10)	—	4 = 16% (10 = 10%)
Anorexia	—	—	—	—	—	—	4 (6)	—	4 (6)	—	4 = 16% (6 = 6%)
Arthralgia	—	—	0	—	2 (3)	—	1 (1)	—	3 (4)	—	3 = 12% (4 = 4%)
Stomatitis/pharyngitis	—	—	1 (1)	—	1 (3)	—	1 (1)	—	3 (5)	—	3 = 12% (5 = 5%)

25 mg/m^2 dose levels, grade 1 to 2 fatigue and grade 1 neurosensory symptoms were common. Neurosensory manifestations consisted principally of acral paresthesia and diminished deep tendon reflexes and discrimination of vibratory sensation. Cumulative neurotoxicity was not apparent in nine patients who received more than three courses at the two higher dose levels. Two patients experienced grade 1 hypersensitivity reactions, characterized by flushing, dizziness, and chest tightness, which did not reoccur on retreatment in the absence of premedication. Alopecia was noted in two patients treated at 25 mg/m^2, one each experiencing grade 1 and 2. Neither onychodystrophy nor fluid retention was observed.

Anticancer activity. Evidence of anticancer activity due to XRP6258 was noted in two patients. An 80-year-old male with prostate cancer metastatic to liver and bones whose disease had progressed through surgical castration, bicalutamide, diethyl stilbestrol, and mitoxantrone and prednisone experienced a reduction in prostate-specific antigen from 62 to 21 ng/mL, decreased disease-related bone pain, and reduction in his target lesion, a lymph node metastasis, which qualified as confirmed partial response after four courses at the 15 mg/m^2 dose level. The patient declined further treatment after his sixth course, at which time his response persisted. A 50-year-old male with hormone- and docetaxel-refractory prostate cancer metastatic to bone and iliac lymph nodes also experienced a partial response after treatment with XRP6258 at the 25 mg/m^2 dose level of XRP6258. His prostate-specific antigen decreased from 415 to 44 ng/mL, and his measurable disease showed a confirmed partial response. Progressive disease was noted after eight courses. In addition, a patient with transitional cell carcinoma of the bladder experienced an unconfirmed partial response, and minor responses (tumor size reduction not meeting criteria for partial response) were observed in one patient each with osteosarcoma and prostate cancer. Twelve (48%) patients had stable disease as their best response for greater than 4 months.

PK and pharmacodynamic evaluation. Blood sampling for PK studies was done in 25 patients, and C_{max} and $AUC_{(0\text{-}48\ h)}$ values were estimated in 23 evaluable subjects. Compartmental PK modeling was done in 23 patients, with 9 and 2 patients having PK data from two and three consecutive courses, respectively. A scatter plot of individual $AUC_{(0\text{-}48\ h)}$ data as a function of XRP6258 dose is shown in Fig. 1A. The relationship between XRP6258 dose and $AUC_{0\text{-}48\ h}$ and C_{max} was proportional. The decrease in plasma concentrations of XRP6258 was best described by a triphasic model. Plasma concentration data and superimposed model fit for a typical individual are depicted in Fig. 1B. Pertinent PK variables, as determined by this model, as a function of dose level are listed in Table 5. The PK behavior in plasma was characterized by a rapid initial phase with a $t_{1/2\lambda1}$ averaging 2.6 ± 1.4 minutes, followed by an intermediate phase with a mean $t_{1/2\lambda2}$ of 1.3 ± 0.6 hours, and a prolonged terminal phase (mean $t_{1/2\lambda3}$, 77.3 ± 45.5 hours). V_{ss} values for XRP6258 were very large (mean, 2,034 ± 1,495 L/m^2), and CL rates were high, averaging 53.5 ± 20.3 L/h (27.3 ± 9.7 L/h/m^2), which represented 61% of hepatic blood flow (87 L/h; ref. 10). The interpatient variability was moderate and estimated at 40.7% of $AUC_{(0\text{-}48\ h)}$ (95% confidence interval, 28.9-69.8). The intrapatient variability for $AUC_{(0\text{-}48\ h)}$ was also relatively low (27.3%; 95% confidence interval, 20.6-40.6%) in 18 patients with at least two courses evaluable for PK. Based on CVs, the total variability in CL values expressed in L/h/m^2 was also moderate (CV, 35%), whereas the variability of terminal half-life and V_{ss} values was higher (CV, 59% and 74%, respectively). CL, expressed in L/h, did not relate well to BSA (R^2 = 0.303; P = 0.0065). However, after correction for the BSA of each individual patient (11), the total variability in the CL of XRP6258 was slightly lower (35.4% versus 38.8%). Indeed, the value for relative reduction in PK variability was 8.8%.

An analysis of PK data from individuals in whom plasma sampling was done during multiple courses showed no apparent changes in CL or $AUC_{(0\text{-}48\ h)}$ with repetitive treatment.

Relationships between PK variables reflecting XRP6258 exposure, such as $AUC_{(0\text{-}48\ h)}$ and C_{max} values, from course 1 and the percent decrements in ANCs were assessed, and scatter plots depicting percentage decrements in ANC as functions of both $AUC_{(0\text{-}48\ h)}$ and C_{max} are depicted in Fig. 1C. Although decrements in the ANC seem to loosely relate to these variables, neither linear nor nonlinear models could be derived to adequately fit these relationships.

Discussion

Primary and acquired tumor resistance limits the effectiveness and spectrum of activity of the taxanes in preclinical and

clinical studies. The synthesis of new taxoids, such as XRP6258, which are poor substrates for P-gp and evade MDR, may be one means to increase both the magnitude and spectrum of activity of this class of agents, as well as enable penetration of these agents into tissues and membranes, such as the central nervous system, in which P-gp pumps may serve as barriers.

Neutropenia was the principal DLT of XRP6258 observed in this study. Although neutropenia was common at the higher dose levels, the duration of severe neutropenia was typically brief and rarely associated with fever. At the recommended dose level, 20 mg/m^2, grade 4 neutropenia was observed in only 4% of courses, which compares favorably to other taxanes. Similar to other taxanes, anemia and thrombocytopenia were rarely observed, even in HP patients. Gastrointestinal toxicities, particularly nausea, vomiting, and diarrhea, were mild to moderate even in the absence of routine prophylaxis and were generally manageable with standard therapies. Diarrhea was observed commonly with XRP6258, with 14 (56%) of 25 patients experiencing diarrhea during 29 (28%) courses and 1 patient experiencing severe (grade 3) diarrhea. XRP6258, a much poorer substrate for the P-gp multidrug transporter pump than docetaxel, may accumulate in enterocytes, which constitutively express P-gp, a characteristic that could explain why this toxicity was so common relative to other taxoids in clinical use (12). Clinically relevant neurotoxicity was negligible, and although the assessment of cumulative neurotoxicity is limited by the refractory nature of the patients, cumulative neurotoxicity was not evident in HP patients receiving more than three courses of treatment. Furthermore, severe hypersensitivity reactions were not evident in the absence of premedication. In contrast to docetaxel, fluid retention was not observed with XRP6258 (2). However, it is recognized that further experience in a larger number of patients is required to more fully characterize the nonhematologic toxicities of XRP6258 and compare these effects with other taxoids.

The PK profile of XRP6258 is similar to that of docetaxel and is characterized by dose proportionality in the dosing range of the present study and triphasic elimination in plasma. There was no evidence of major changes in the PK behavior of XRP6258, suggesting the absence of autoinduction or drug accumulation in plasma after cumulative treatment in patients in whom plasma sampling was done during multiple courses. The volume of distribution at steady state for XRP6258 seems larger than that of docetaxel (mean V_{ss} values, 2,034 $\pm$ 1,495 versus 83.2 L/m^2), and its terminal half-life is longer (mean $t_{1/2\lambda 3}$, 77.3 $\pm$ 45.5 versus 11.2 hours, respectively; ref. 13). These differences are probably due, at least in part, to the lower limit of quantitation of XRP6258. Alternative explanations could be the low recognition by P-gp compared with docetaxel and the presence of a deep compartment. The

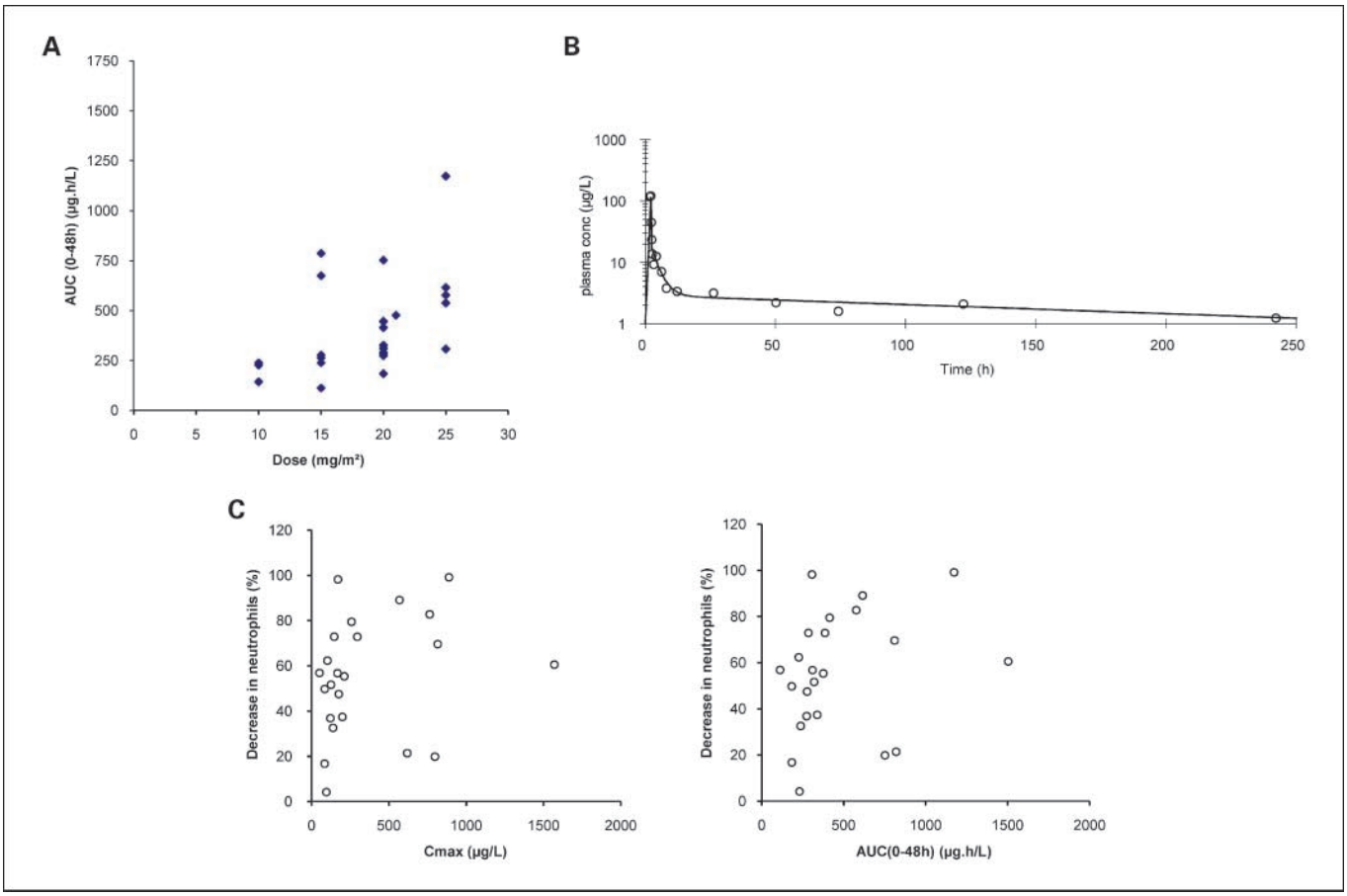

Fig. 1. PK data. *A,* scatter plot of individual first-cycle XRP6258 $AUC_{(0\text{-}48\ h)}$ values as a function of dose level (n = 25). *B,* representative plasma total XRP6258 concentration-time profile of one patient treated with a 1-h i.v. infusion at 20 mg/m^2 [○, observed value; -, fitted value (three-compartment model)]. *C,* scatter plots depicting percent decrements in ANC as a function of XRP6258 $AUC_{(0\text{-}48\ h)}$ values (*left*) and observed C_{max} values in the first cycle (n = 23).

Table 5. PK variables of XRP6258

Dose (mg/m^2)	No. patients	PK variables (data expressed as mean ± SD)					
		C_{max} (μg/L)*	$AUC_{(0-48\ h)}$ (μg.h/L)*	AUC (μg.h/L) †	$t_{1/2\lambda3}$ (h) †	CL (L/h/m^2) †	V_{ss} (L/m^2) †
10	3	75.8 ± 31.7	203 ± 52	361 ± 128	50.7 ± 14.2	30.1 ± 11.2	1,623 ± 533
15	6	287 ± 273	392 ± 271	745 ± 215	55.2 ± 35.6	21.3 ± 6.0	1,266 ± 1,255
20	9 ‡	222 ± 207	373 ± 157	766 ± 306	95.6 ± 53.4	29.7 ± 12.1	2,637 ± 1,657
21§	1	487	477	687	41.0	30.4	547
25	4	535 ± 305	642 ± 320	1,038 ± 299	81.9 ± 41.4	25.0 ± 5.6	1,985 ± 1,615
Overall	23	—	—	—	77.3 ± 45.5	27.3 ± 9.7	2,034 ± 1,495

*Noncompartmental analysis.
† Individual modeling.
‡ One patient treated at 25 mg/m^2 was not evaluable for PK but was treated at 20 mg/m^2 at the second cycle.
§ One patient included in the 25 mg/m^2 cohort was found to have a high BSA (2.53 m^2); therefore, treatment was done with dose adjustment based on a restricted BSA of 2.1 m^2, and subsequently, he only received a dose of 21 mg/m^2.

CL seemed to be correlated to the BSA. However, the relative reduction in PK variability following BSA correction was low in this study and will need to be confirmed in a larger number of patients.

Several novel taxanes have undergone clinical development to increase the effectiveness and decrease the toxicity of this class of cytotoxics (14–20). XRP6258 is at least as effective as docetaxel in most of the preclinical models and shows greater antitumor activity in xenografts exhibiting primary resistance to taxanes, such as the P388 i.p. leukemia model. Moreover, broader antitumor spectra may result from the lower affinity of XRP6258 for P-gp, which has been well documented in preclinical models. The relevance of this relative advantage in a clinical setting, although supported by the preliminary antitumor activity reported in our study, including in tumors resistant to taxanes, such as osteosarcoma (21), or with acquired resistance following taxane treatment, still needs to be confirmed. Similarly, clinical evidence for robust activity in primary or secondary central nervous system tumors is necessary to confirm the preliminary evidence of blood-brain barrier penetration, which could justify further clinical development. The linear PK profile of XRP6258, although similar to that of docetaxel, showed relatively low intrapatient and interpatient variability over the studied range, suggesting predictable toxicity. With regard to the tolerance and administration profile, XRP6258 seems advantageous when compared with docetaxel and paclitaxel. Its solubility is comparable with that of docetaxel, allowing a polysorbate-based formulation that does not require cremophor and, therefore, results in reduced incidence of hypersensitivity reaction. Based on the results of this study, XRP6258 administration does not require premedication, thus resulting in significant administration and convenience advantages. An acceptable toxicity profile, mainly the low neurotoxicity and manageable hematologic toxicity at the recommended dose on this schedule, as well as the low incidence of fluid retention and alopecia, also favors XRP6258.

In conclusion, XRP6258 is a new taxane characterized by convenient administration with less premedication, linear PKs, and a favorable safety profile for hematologic toxicity and hypersensitivity reaction. XRP6258 is a weak P-gp substrate in preclinical models, which seems to correlate with a greater potency and possibly an extended spectrum of antitumor activity in the clinic, including those patients who have shown taxane resistance. Therefore, the results of this study support broad disease-directed evaluations of XRP6258 on this administration schedule, which are ongoing.

Disclosure of Potential Conflicts of Interest

Consulting agreements for A.W. Tolcher: Abraxis; Adnexus (formerly Compound Therapeutics); Amgen; Anandys; Ariad Pharmaceuticals, Inc.; AstraZeneca; Astellas; Biogen Idec, Inc.; Centocor; Chemokine; Curis; Cytokinetics; Dendreon Corp.; Eli Lilly; Enzon; Exelixis; Fibrogen; Five Prime Therapeutics, Inc.; Genentech; Genetics Squared; Genta; Geron; HUYA Bioscience International; Immunogen; Johnson & Johnson; Merck; MGI Pharma, Inc.; Micromet; NCI Drug Development Group; Nektar; Nereus; Micromet; Nervianoms; Onyx Pharmaceuticals; Paramount Biosciences, LLC; Pfizer; Sankyo; Sanofi-Aventis; Santaris; Schering-Plough; Spectrum; Symphogen; Supergen; and Takeda.

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ORIGINAL ARTICLE

Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer

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ABSTRACT

BACKGROUND

Mitoxantrone plus prednisone reduces pain and improves the quality of life in men with advanced, hormone-refractory prostate cancer, but it does not improve survival. We compared such treatment with docetaxel plus prednisone in men with this disease.

METHODS

From March 2000 through June 2002, 1006 men with metastatic hormone-refractory prostate cancer received 5 mg of prednisone twice daily and were randomly assigned to receive 12 mg of mitoxantrone per square meter of body-surface area every three weeks, 75 mg of docetaxel per square meter every three weeks, or 30 mg of docetaxel per square meter weekly for five of every six weeks. The primary end point was overall survival. Secondary end points were pain, prostate-specific antigen (PSA) levels, and the quality of life. All statistical comparisons were against mitoxantrone.

RESULTS

As compared with the men in the mitoxantrone group, men in the group given docetaxel every three weeks had a hazard ratio for death of 0.76 (95 percent confidence interval, 0.62 to 0.94; P=0.009 by the stratified log-rank test) and those given weekly docetaxel had a hazard ratio for death of 0.91 (95 percent confidence interval, 0.75 to 1.11; P=0.36). The median survival was 16.5 months in the mitoxantrone group, 18.9 months in the group given docetaxel every 3 weeks, and 17.4 months in the group given weekly docetaxel. Among these three groups, 32 percent, 45 percent, and 48 percent of men, respectively, had at least a 50 percent decrease in the serum PSA level (P<0.001 for both comparisons with mitoxantrone); 22 percent, 35 percent (P=0.01), and 31 percent (P=0.08) had predefined reductions in pain; and 13 percent, 22 percent (P=0.009), and 23 percent (P=0.005) had improvements in the quality of life. Adverse events were also more common in the groups that received docetaxel.

CONCLUSIONS

When given with prednisone, treatment with docetaxel every three weeks led to superior survival and improved rates of response in terms of pain, serum PSA level, and quality of life, as compared with mitoxantrone plus prednisone.

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Prostate cancer is the most common cancer among men, with approximately 220,000 cases and 29,000 deaths annually in the United States.[1] About 10 to 20 percent of men with prostate cancer present with metastatic disease, and in many others, metastases develop despite treatment with surgery or radiotherapy.

Treatment of metastatic prostate cancer is palliative. In about 80 percent of men, primary androgen ablation leads to symptomatic improvement and a reduction in serum levels of prostate-specific antigen (PSA), but in all patients the disease eventually becomes refractory to hormone treatment. The options then include symptomatic care with narcotic analgesics, radiotherapy to dominant sites of bone pain, treatment with bone-seeking isotopes such as strontium-89, and cytotoxic chemotherapy. Bisphosphonates may reduce skeletal complications,[2-4] and low-dose prednisone or hydrocortisone may be palliative in some patients.[5,6]

Chemotherapy can reduce serum PSA levels in patients with hormone-refractory prostate cancer and relieves pain in some patients, but tolerability is of concern, particularly since most patients are elderly and many have other medical problems.[7] A randomized trial showed that mitoxantrone plus low-dose prednisone relieved pain and improved the quality of life more frequently than did prednisone alone.[8,9] Consistent benefits of mitoxantrone plus a corticosteroid were observed in other randomized trials, but none found that this approach improved survival.[10-12] These trials established mitoxantrone plus a corticosteroid as the treatment of reference for hormone-refractory prostate cancer.

Phase 2 studies of the taxane docetaxel have reported PSA responses (defined as a reduction in serum PSA levels of at least 50 percent) in up to 50 percent of patients.[13-16] Studies of docetaxel plus either estramustine or calcitriol have shown PSA responses in up to 80 percent of patients.[17-19] However, outcomes of single-group studies are subject to bias.[20]

We conducted a phase 3 study, the TAX 327 Study, comparing docetaxel (given either every three weeks or weekly) plus daily prednisone with mitoxantrone plus prednisone. The docetaxel regimens were selected on the basis of their dose equivalence (a dose intensity of 25 mg per square meter of body-surface area per week and a maximal cumulative dose of 750 mg per square meter) and their activity and tolerability in phase 2 studies. The primary hypothesis was that treatment with docetaxel plus prednisone would improve overall survival as compared with mitoxantrone plus prednisone.

METHODS

PATIENTS

This randomized, nonblinded, phase 3 study involved centers in 24 countries. Eligible patients had histologically or cytologically confirmed adenocarcinoma of the prostate with clinical or radiologic evidence of metastatic disease, had had disease progression during hormonal therapy, and were receiving primary androgen-ablation therapy as maintenance therapy. At least four weeks had to have elapsed between the withdrawal of antiandrogens (six weeks in the case of bicalutamide) and enrollment, so as to avoid the possibility of confounding as a result of the response to antiandrogen withdrawal.[21,22] Another requirement was disease progression, as indicated by increasing serum levels of PSA on three consecutive measurements obtained at least one week apart or findings on physical examination or imaging studies.

Eligible patients had a Karnofsky performance-status score of at least 60 percent, no prior treatment with cytotoxic agents (except estramustine) or radioisotopes, no history of another cancer within the preceding five years (except basal or squamous-cell skin cancer), no brain or leptomeningeal metastases, no symptomatic peripheral neuropathy of grade 2 or higher, and no other serious medical condition. At least four weeks had to have elapsed between prior surgery or radiotherapy (limited to no more than 25 percent of the bone marrow) and enrollment. Prior treatment with corticosteroids was allowed. Normal cardiac function was required. Laboratory criteria for eligibility included a neutrophil count of at least 1500 per cubic millimeter, a hemoglobin level of at least 10.0 g per deciliter, a platelet count of at least 100,000 per cubic millimeter, a total bilirubin level below the upper limit of the normal range for each institution, and serum alanine aminotransferase, aspartate aminotransferase, and creatinine levels that were no more than 1.5 times the upper limit of the normal range.

A clinical history was obtained, and a physical examination, with radiographic imaging, computed tomography, and bone scanning, was performed within 14 days before randomization. Blood tests including measurement of serum PSA, electrocardiography, and an evaluation of the left ventricular ejection fraction by means of a multiple gated

acquisition scan or echocardiography were performed. Pain, analgesic intake, and the quality of life were assessed at baseline. Pain was assessed by means of the Present Pain Intensity (PPI) scale from the McGill–Melzack questionnaire, which uses verbal descriptors; scores can range from 0 to 5, with higher scores indicating greater pain.[23] Patients recorded their daily PPI score and analgesic use in a diary. A daily analgesic score was calculated by assigning a score of 4 for a standard dose of a narcotic analgesic (e.g., 10 mg of morphine) and a score of 1 for a standard dose of a nonnarcotic analgesic. Patients were required to have stable levels of pain for at least seven days before randomization, defined by a daily variation of no more than 1 in the PPI score or of no more than 25 percent in the analgesic score. The quality of life was assessed with the Functional Assessment of Cancer Therapy–Prostate (FACT-P) questionnaire; scores on this self-administered questionnaire can range from 0 to 156, with higher scores indicating a better quality of life.[24,25]

All patients provided written informed consent, and the study was approved by all institutional review boards in accordance with the international standards of good clinical practice. An independent data and safety monitoring committee was established.

RANDOMIZATION AND TREATMENT

Randomization was centralized with the use of a stratified, permuted-block allocation scheme according to the baseline pain level (pain was classified as present, as defined by a median PPI score of at least 2 or a mean analgesic score of at least 10, or as absent, as defined by a median PPI score of less than 2 and a mean analgesic score of less than 10) and the baseline Karnofsky performance-status score (70 percent or less vs. 80 percent or more). Patients who were randomly assigned to the docetaxel groups received either 75 mg of docetaxel (Taxotere, Aventis) per square meter as a 1-hour intravenous infusion on day 1 every 21 days or 30 mg of docetaxel per square meter as a 30-minute intravenous infusion on days 1, 8, 15, 22, and 29 of a 6-week cycle. Patients who were randomly assigned to the standard-therapy group received 12 mg of mitoxantrone (Novantrone, Immunex and Wyeth–Ayerst) per square meter as a 30-minute infusion on day 1 every 21 days. All patients received 5 mg of prednisone (or prednisolone, if prednisone was not available) orally twice daily starting on day 1. Premedication with dexamethasone was required in the docetaxel groups (8 mg given 12 hours, 3 hours, and 1 hour before the docetaxel infusion in the group treated every three weeks and 8 mg given 1 hour before docetaxel in the group treated weekly). Antiemetic medication was prescribed according to local practice.

Up to 10 cycles of treatment were planned for the group given docetaxel every three weeks and the mitoxantrone group and up to 5 cycles (of six weeks each) in the weekly-docetaxel group. Treatment delays of up to two weeks and up to two dose reductions were allowed. Dose reductions were specified for patients who had had grade 4 neutropenia for at least seven days, an infection, or grade 3 or 4 neutropenia with an oral temperature of at least 38.5°C. A dose reduction or treatment delay was also stipulated for patients who had an absolute neutrophil count of less than 1500 per cubic millimeter (for those on three-week schedules) or less than 1000 per cubic millimeter (for those receiving weekly docetaxel) on a treatment day and for those with grade 3 or 4 thrombocytopenia. Treatment with granulocyte colony-stimulating factor was allowed for patients with febrile neutropenia. Systemic corticosteroids (other than dexamethasone and prednisone) and bisphosphonates were not permitted.

FOLLOW-UP AND OUTCOMES

Physical examinations and baseline blood tests were repeated at three-week intervals. Imaging studies to determine the extent of disease were performed at intervals of six to nine weeks and repeated after four weeks to identify those with a response.

The primary end point was overall survival. Secondary end points were predefined reductions in pain, an improvement in the quality of life, a reduction in serum PSA levels of at least 50 percent, and objective tumor responses.

Patients with a PPI score of at least 2, an analgesic score of at least 10, or both (averaged over the previous week) at baseline were assessed for the pain response at three-week intervals. A pain response was defined as a two-point reduction in the PPI score from baseline without an increase in the analgesic score or as a reduction of at least 50 percent in the analgesic score without an increase in the PPI score, either of which was maintained for at least three weeks. Pain progression was defined as an increase in the PPI score of at least one point from the nadir, an increase from baseline of at least

25 percent in the analgesic score, or a requirement for palliative radiotherapy.

Serum PSA was measured every three weeks, and a response (for patients with a baseline PSA level of at least 20 ng per milliliter) was defined as a reduction from baseline of at least 50 percent that was maintained for at least three weeks, whereas PSA progression was defined as an increase from the nadir of either at least 25 percent for men with no PSA response or at least 50 percent for all others. The duration of the PSA response and the pain response was defined as the time between the first and last evaluations at which the response criteria were met. For patients with at least one bidimensionally measurable lesion, tumor response was evaluated with the use of World Health Organization criteria.[26]

The quality of life was assessed with the FACT-P questionnaire at baseline, every three weeks during therapy, and every month after the completion of therapy. All patients who answered the questionnaire at baseline were included in the evaluation, and the FACT-P score was compared with the baseline value for each of these patients. Patients were defined as having a quality-of-life response if they had a 16-point improvement in their FACT-P score, as compared with baseline, on two measurements obtained at least three weeks apart.

Adverse events were classified according to the Common Toxicity Criteria of the National Cancer Institute (version 2). Serious adverse events were fatal or life-threatening, required or prolonged hospitalization, resulted in persistent or substantial disability or incapacity, or were considered important medical events. Treatment was stopped for any of the following reasons: completion of planned treatment, progression of disease, severe adverse events, or withdrawal of consent.

STATISTICAL ANALYSIS

There were three comparisons of interest between the docetaxel and mitoxantrone groups: docetaxel given every three weeks was compared with mitoxantrone, weekly docetaxel was compared with mitoxantrone, and the combined docetaxel groups were compared with mitoxantrone. The study was designed to detect with 90 percent power a hazard ratio of 0.75 for death in the docetaxel groups as compared with the mitoxantrone group, with a two-sided type I error of 0.05 and with the data analyzed according to the intention to treat. The sample size was established as 1002 patients, and analysis was planned after 535 deaths had occurred. To allow for multiple comparisons, a P value of 0.04 was considered to indicate statistical significance for the comparison of the combined docetaxel groups with the mitoxantrone group, and a P value of 0.0175 was considered to indicate statistical significance for the comparison of each docetaxel group with the mitoxantrone group (all P values were two-sided), thus ensuring an overall significance level of 0.05.

In the primary analysis, overall survival was analyzed by means of the Kaplan–Meier method, with log-rank comparisons stratified according to the level of pain and the Karnofsky performance-status score. Pain, PSA, tumor, and quality-of-life responses were compared by means of the Cochran–Mantel–Haenszel test. All randomized patients were included in the analysis of survival, and all treated patients were included in the evaluation of adverse effects.

Hazard ratios for death were calculated after adjustment for any chance imbalance in potential prognostic factors between the groups. The following factors were entered into a full stratified Cox proportional-hazards model and a backward selection model in which nonsignificant factors were eliminated sequentially at a P level of 0.10: age (less than 65 years vs. 65 years or older); visceral involvement (yes vs. no); liver involvement (yes vs. no); number of prior hormonal therapies (two or fewer vs. more than two); prior estramustine (yes vs. no); presence of rising serum PSA levels alone, as compared with the presence of other indications of progression; baseline hemoglobin level; and baseline serum level of alkaline phosphatase. One planned interim analysis of safety was conducted after the recruitment of 120 patients. No interim analysis for efficacy was performed.

The study was designed by Dr. Tannock in collaboration with Aventis personnel, and the protocol was finalized after being reviewed by the other study cochairs, Drs. de Wit and Eisenberger. The data were collected and maintained by Aventis, but the cochairs handled all questions regarding the management of the study. Only the data and safety monitoring committee saw the results of the interim safety analysis; no analysis was undertaken nor were the results seen by Aventis, the study cochairs, or any other investigator until the predefined number of events had occurred. The protocol contained a plan for analysis and publication at that time. All data were provided to the cochairs at the comple-

tion of the study. Aventis personnel undertook the statistical analysis. The article was drafted by Dr. Tannock and modified after being reviewed by the cochairs and other coauthors. Aventis reviewed the manuscript, but its final content was entirely determined by the investigators.

RESULTS

CHARACTERISTICS OF THE PATIENTS AND TREATMENT

A total of 1006 patients underwent randomization from March 2000 through June 2002. The da-

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Docetaxel Every 3 Wk	Weekly Docetaxel	Mitoxantrone Every 3 Wk
No. randomized	335	334	337
Ineligible (%)	12	12	12
Age			
Median (yr)	68	69	68
Range (yr)	42–92	36–92	43–86
≥75 Yr (%)	20	21	20
Gleason score (%)			
≤7	42	40	42
8–10	31	31	28
Not available	26	29	30
Prior treatment (%)			
Prostatectomy	19	24	21
Radiotherapy	52	44	51
Estramustine	19	18	20
Hormonal manipulations (%)†			
1	9	8	6
2	68	72	69
>2	23	21	25
Karnofsky performance-status score ≤70% (%)	13	12	14
Pain (%)‡	45	45	46
Serum PSA			
Median (ng/ml)	114	108	123
≥20 ng/ml (%)	87	84	89
Extent of disease (%)			
Bone metastases	90	91	92
Visceral disease	22	24	22
Measurable lesions	40	39	40
Evidence of progression at entry (%)§			
Bone scan	71	69	69
Increase in measurable lesions	28	30	28
Increase in nonmeasurable lesions	13	16	15
Increased PSA	72	66	68

* All patients were included in the intention-to-treat analysis. Because of rounding, not all percentages total 100.
† Hormonal manipulation was defined as bilateral orchiectomy or hormone therapy.
‡ Pain was defined by a score of 2 or more on the Present Pain Intensity scale or an analgesic score of at least 10.
§ Patients may have more than one indication for progression of disease.

tabase was locked on August 6, 2003, after the requisite number of deaths, specified in the statistical plan, had occurred.

The baseline characteristics of the patients were well balanced among the three treatment groups (Table 1). The median age was 68 years; about 20 percent of the patients were at least 75 years old. About 45 percent had pain, and about 40 percent had measurable soft-tissue lesions. The most common indicators of disease progression before study entry were an increasing serum PSA level and evidence of an increase in bone metastases on bone scanning.

Only nine patients (1 percent) did not receive chemotherapy and prednisone (Table 2). Patients tended to receive more cycles of the regimen in which docetaxel was given every three weeks than of the regimen in which mitoxantrone was given every three weeks. Most patients received the prescribed doses on schedule, with 8 to 12 percent requiring a dose reduction and 21 to 34 percent requiring at least one chemotherapy infusion to be delayed. Twenty percent of the patients who were randomly assigned to receive mitoxantrone subsequently received docetaxel, and 27 percent of those in the group given docetaxel every three weeks received subsequent mitoxantrone, as did 24 percent of those in the weekly-docetaxel group.

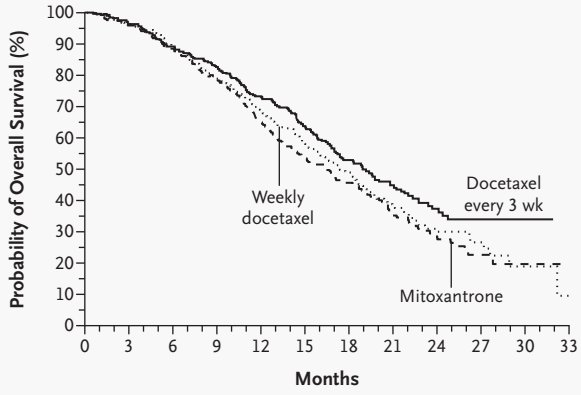
Table 2. Treatment.*

Variable	Docetaxel Every 3 Wk	Weekly Docetaxel	Mitoxantrone Every 3 Wk
No. randomized	335	334	337
No. treated with chemotherapy	332	330	335
No. treated with prednisone	332	330	335
No. of cycles			
Median	9.5	4	5
Range	1–11	1–6	1–11
≥1 Infusion delayed (%)	24	34	21
Dose reduction (%)	12	9	8
Major protocol violation (%)	7	8	7
Reasons for stopping treatment (%)			
Completed treatment	46	35	25
Progression of disease	38	35	56
Adverse event	11	16	10
Withdrawal of consent	1	6	3
Death	1	2	2
Other	4	6	5
Crossover to other drug (%)	27	24	20

* Percentages relate to the number of patients treated in each group. Because of rounding, not all percentages total 100.

EFFICACY

The median duration of follow-up was similar among the three groups: 20.8 months in the group given docetaxel every 3 weeks and 20.7 months in the other two groups. There were 166 deaths (50 percent; hazard ratio for death, 0.76; 95 percent confidence interval, 0.62 to 0.94) in the group given docetaxel every three weeks and 190 deaths (57 percent; hazard ratio, 0.91; 95 percent confidence interval, 0.75 to 1.11) in the group given weekly docetaxel, as compared with 201 deaths (60 percent) in the mitoxantrone group. When the two docetaxel groups were combined and compared with the mitoxantrone group, the hazard ratio for death was 0.83 (95 percent confidence interval, 0.70 to 0.99; P=0.04). As compared with the survival rate in the mitoxantrone group, the survival rate was significantly higher (P=0.009) in the group given docetaxel every three weeks but not in the group given weekly docetaxel (P=0.36). The median duration of survival was 18.9 months (95 percent confidence interval, 17.0 to 21.2) in the group given docetaxel every 3 weeks, 17.4 months (95 per-



No. at Risk

Docetaxel every 3 wk	335	296	217	104	37	5
Weekly docetaxel	334	297	200	105	29	4
Mitoxantrone	337	297	192	95	29	3

Figure 1. Kaplan–Meier Estimates of the Probability of Overall Survival in the Three Groups.

Table 3. Response to Treatment, as Measured by Decreases in Pain, PSA Level, and Tumor Burden and Improvements in the Quality of Life.*

Variable	Docetaxel Every 3 Wk	Weekly Docetaxel	Mitoxantrone Every 3 Wk
Pain†			
No. who could be evaluated	153	154	157
Response (%)			
Rate	35	31	22
95% CI	27–43	24–39	16–29
P value	0.01	0.08	
Duration (mo)‡			
Median	3.5	5.6	4.8
95% CI	2.4–8.1	2.8–6.8	4.4–indeterminate
≥50% Reduction in serum PSA			
No. who could be evaluated	291	282	300
Response (%)			
Rate	45	48	32
95% CI	40–51	42–54	26–37
P value	<0.001	<0.001	
Duration (mo)‡			
Median	7.7	8.2	7.8
95% CI	7.1–8.6	6.3–11.5	5.4–10.5
Tumor response			
No. who could be evaluated	141	134	137
Response (%)			
Rate	12	8	7
95% CI	7–19	4–14	3–12
P value	0.11	0.59	
Quality of life			
No. who could be evaluated	278	270	267
Response (%)§			
Rate	22	23	13
95% CI	17–27	18–28	9–18
P value	0.009	0.005	

* P values are for comparisons with the mitoxantrone group. CI denotes confidence interval.

† A pain response was defined as a two-point reduction in the Present Pain Intensity (PPI) score without an increase in the analgesic score or a reduction of at least 50 percent in the analgesic score without an increase in the PPI score, which was maintained for at least three weeks.

‡ Data on 54 percent and 63 percent of patients were censored in the Kaplan–Meier analysis of the median duration of pain and PSA response, respectively. The chief reason for data censoring was further antitumor therapy after progression of disease as defined by other criteria.

§ A response was defined by a 16-point improvement from baseline in the Functional Assessment of Cancer Therapy–Prostate (FACT-P) score on two measurements obtained at least three weeks apart.

cent confidence interval, 15.7 to 19.0) in the group given weekly docetaxel, and 16.5 months (95 percent confidence interval, 14.4 to 18.6) in the mitoxantrone group. Kaplan–Meier survival curves for the three groups are shown in Figure 1.

The result of the sensitivity analysis, in which survival was adjusted for possible imbalances in potential prognostic factors, was consistent with the primary result. The hazard ratio for death in the group given docetaxel every three weeks, as compared with the mitoxantrone group, was 0.76 without adjustment and 0.74 and 0.75 after adjustment in the full stratified and backward Cox proportional-hazards models, respectively. As expected, visceral involvement, a high baseline alkaline phosphatase level, and a low hemoglobin level were negative prognostic factors in the multivariate models, whereas a rising serum PSA as the sole indicator of progression was a favorable factor. Post hoc analysis indicated that a high Gleason score (8, 9, or 10) was an adverse prognostic factor for survival. The survival benefit of docetaxel given every three weeks was consistent across subgroups defined according to the presence or absence of pain at baseline, the Karnofsky performance-status score (70 percent or less vs. 80 percent or more), and age (younger than 65 years vs. 65 years or older) (data not shown).

A reduction in pain was more frequent among patients receiving docetaxel every three weeks than among those treated with mitoxantrone (35 percent vs. 22 percent, P=0.01) (Table 3), but the percentage of patients with reduced pain in the weekly docetaxel group (31 percent) did not differ significantly from that of the mitoxantrone group. The median duration of reduced pain was 3.5 to 5.6 months and did not differ significantly among the groups.

Rates of PSA response were significantly higher in the docetaxel groups (45 percent in the group given docetaxel every three weeks and 48 percent in the group given weekly docetaxel, P<0.001 for both comparisons) than in the mitoxantrone group (32 percent) (Table 3). The median duration of the PSA response ranged from 7.7 to 8.2 months and did not differ significantly among the three groups.

Although patients with measurable soft-tissue lesions who received docetaxel every three weeks had a somewhat higher rate of tumor response than such patients who received mitoxantrone every three weeks (12 percent vs. 7 percent, P=0.11), this difference was not significant (Table 3).

ADVERSE EVENTS

The incidence of grade 3 and 4 neutropenia was relatively low, and febrile neutropenia was rare (Table 4). Two patients died from sepsis during treatment, one in the docetaxel group and one in the mitoxantrone group. There was a higher incidence of cardiac events among patients who received mitoxantrone (Table 4). Most other types of adverse events were more frequent among patients receiving docetaxel, and there was no trend toward a lower frequency with weekly docetaxel than with docetaxel given every three weeks. Low-grade adverse events that occurred in at least 15 percent of patients in one of the groups included fatigue, nausea or vomiting or both, alopecia, diarrhea, nail changes, sensory neuropathy, anorexia, changes in taste, stomatitis, dyspnea, tearing, peripheral edema, and epistaxis (Table 4). More patients in the docetaxel groups than in the mitoxantrone group had at least one serious adverse event, with rates of 26 percent among those in the group given docetaxel every three weeks, 29 percent among those given weekly docetaxel, and 20 percent among those given mitoxantrone. Five deaths were probably related to treatment, three of them in the mitoxantrone group.

More patients in the mitoxantrone group stopped treatment because of disease progression than was the case in the docetaxel groups, and more stopped treatment because of completion of treatment or adverse events in the docetaxel groups (Table 2). Adverse events that led to the discontinuation of treatment included fatigue, musculoskeletal or nail changes, sensory neuropathy, and infection in the docetaxel groups and cardiac dysfunction in the mitoxantrone group.

Table 4. Adverse Events of Any Grade, or of Grade 3 or 4, That Occurred or Worsened during Treatment.

Adverse Event	Docetaxel Every 3 Wk (N=332)	Weekly Docetaxel (N=330)	Mitoxantrone Every 3 Wk (N=335)
		percent	
Grade 3 or 4 anemia	5	5	2
Grade 3 or 4 thrombocytopenia	1	0	1
Grade 3 or 4 neutropenia	32*	2†	22
Febrile neutropenia	3	0	2
Impaired LVEF‡	10†	8†	22
Major decrease	1†	2*	7
Fatigue	53†	49†	35
Grade 3 or 4	5	5	5
Alopecia	65†	50†	13
Nausea, vomiting, or both	42	41	38
Diarrhea	32†	34†	10
Nail changes	30†	37†	7
Sensory neuropathy	30†	24†	7
Anorexia	17	21*	14
Change in taste	18†	24†	7
Stomatitis	20†	17†	8
Myalgia	14	14	13
Dyspnea	15*	14*	9
Tearing	10†	21†	1
Peripheral edema	19†	12†	1
Epistaxis	6	17†	2
≥1 Serious adverse event	26	29	20
Treatment-related death	0.3	0.3	1

* P≤0.05 by Fisher's exact test for the comparison with the mitoxantrone group.
† P≤0.0015 by Fisher's exact test for the comparison with the mitoxantrone group. A Bonferroni adjustment for multiplicity was used to obtain the nominal significance level of 0.0015 (approximately 0.05÷34), on the basis of two tests being carried out on the 17 adverse events, with at least 20 events in at least one of the three treatment groups.
‡ A major decrease in the left ventricular ejection fraction (LVEF) was defined as a decrease of at least 10 percent in the absolute value to below the lower limit of the normal range.

QUALITY OF LIFE

The quality of life was evaluated in 815 patients, a group that made up the intention-to-treat population from countries in which a local translation of the FACT-P was available (Table 3). The percentage of patients who had an improvement in the quality of life was similar in the two docetaxel groups (22 percent in the group given docetaxel every three weeks and 23 percent in the group given weekly docetaxel) and significantly higher than that in the mitoxantrone group (13 percent; P=0.009 and P=0.005, respectively). Figure 2 shows the greatest changes in the scores and the median changes in the scores for individual domains of the FACT-P during treatment. The greatest benefit in the docetaxel groups was in the subscale representing prostate-specific concerns (including weight loss, appetite, pain, physical comfort, and bowel and genitourinary function).

DISCUSSION

In this phase 3 study, two schedules of docetaxel administered with prednisone were compared with mitoxantrone plus prednisone, the standard chemotherapy for hormone-refractory prostate cancer. The median overall survival was higher for the group that received docetaxel every three weeks

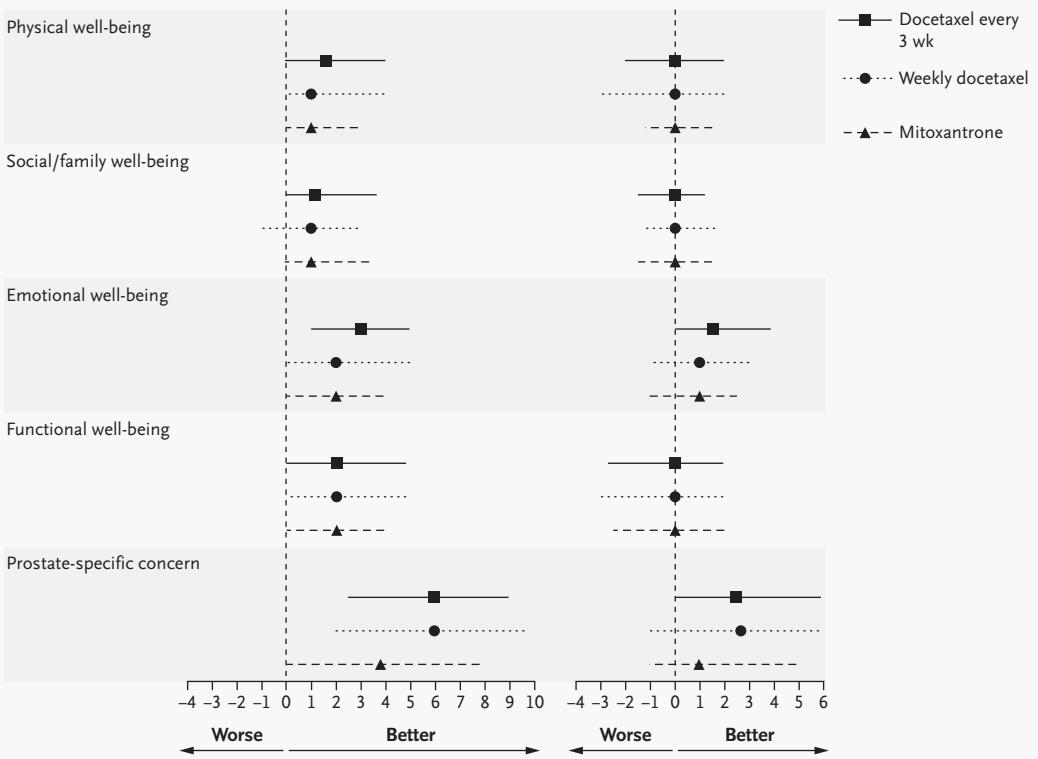


Figure 2. Greatest Change and Median Change from Baseline in Normalized Scores on the Functional Assessment of Cancer Therapy–Prostate Questionnaire for Individual Domains of the Quality of Life during Treatment.

than for the mitoxantrone group, but not for the group that received weekly docetaxel. These differences were not influenced by adjustment for potential prognostic factors, and there were consistent trends in survival in the intention-to-treat population and in various subgroups. Overall, as compared with the mitoxantrone group, the docetaxel groups had better pain control and quality of life and more frequent PSA responses, but at the cost of a higher incidence of adverse effects.

The characteristics of the patients in this study are typical of those seen in oncology practices. Most patients were elderly and had received at least two types of hormonal manipulation. Most had bone metastases and a high serum PSA level, and about half had substantial pain. All these patients had a short life expectancy. Four published phase 3 studies have evaluated mitoxantrone plus prednisone for hormone-refractory prostate cancer.[9-12] In our study, patients in the mitoxantrone group had a PSA response rate of 32 percent and a rate of predefined reduction in pain of 22 percent. In prior studies of symptomatic patients alone, mitoxantrone plus prednisone resulted in PSA response rates of 34 percent[9] and 29 percent,[12] whereas one study of asymptomatic patients reported a 48 percent response rate.[10] Rates of reduction in pain of 38 percent[9] and 39 percent[12] have been reported, but these studies used less strict response criteria than we did. The median survival among patients in the mitoxantrone group in our study was 16.5 months, as compared with 10 to 12.5 months in the Canadian and Cancer and Leukemia Group B studies[9,11,12] and 21 months in a study of asymptomatic patients.[10] Mitoxantrone plus prednisone remains an appropriate treatment for patients with hormone-refractory prostate cancer who might be susceptible to the toxic effects of docetaxel. However, treatment with mitoxantrone plus a corticosteroid has not improved survival over that afforded by a corticosteroid alone.[9-11]

Previous experience with docetaxel in the treat-

ment of hormone-refractory prostate cancer is limited to phase 2 studies. The PSA response ranged from 38 to 46 percent for docetaxel alone[13-16] and up to 80 percent for docetaxel combined with estramustine or calcitriol.[17-19] The rate of objective reduction in pain after treatment with docetaxel alone was 48 percent in the only study that evaluated pain.[13] In our study, the rates of PSA response were 45 percent in the group given docetaxel every three weeks and 48 percent in the group given weekly docetaxel, and the respective rates of predefined (and stringent) reductions in pain were 35 percent and 31 percent, all of which, except for the response of pain in the weekly-docetaxel group, were significantly higher than the rates in the mitoxantrone group. More important, we found a significant improvement in overall survival for docetaxel as compared with mitoxantrone. A similar improvement in survival for docetaxel plus estramustine in comparison with mitoxantrone plus prednisone was found in a phase 3 study by the Southwest Oncology Group that is reported in this issue of the *Journal*.[27]

Safe use of docetaxel requires premedication with dexamethasone. Since the docetaxel group received about twice the dose of corticosteroids that the mitoxantrone group received, the better results in the docetaxel group may have been due in part to the higher dose of corticosteroids.[5,6,9-11] This seems unlikely because with prednisone or hydrocortisone alone, the rate of PSA response in large phase 3 studies was in the range of 16 to 24 percent and was generally transient.[5,9-11,28] In symptomatic patients, prednisone or hydrocortisone treatment was inferior to chemotherapy plus corticosteroid in reducing pain and other symptoms.[9,10,28] Intensive treatment with dexamethasone was reported to have no effect on hormone-refractory prostate cancer in one small study.[29]

Serious adverse events occurred among 26 percent of patients in the group given docetaxel every three weeks and 29 percent of the group given weekly docetaxel, as compared with 20 percent in the mitoxantrone group. However, hematologic events were rare in all three groups, and most patients received the prescribed doses of the assigned drug on schedule. Although neutropenia was most common in the group given docetaxel every three weeks, infection was rare. There was a higher incidence of cardiotoxicity in the mitoxantrone group, but it was rarely of clinical importance. Most adverse events associated with docetaxel were of low grade and were bothersome rather than life-threatening; loss of sensation in the fingers and toes proved particularly annoying to some patients.

We designed this study to include a schedule with lower doses of docetaxel given weekly to assess whether a weekly regimen was better tolerated than treatment every three weeks. We found no evidence of a lower rate of adverse events or improved outcomes with the weekly schedule. Treatments given at intervals of three weeks are more convenient for most patients and we think should remain the standard with docetaxel.

Significantly more patients satisfied the stringent criterion of a 16-point improvement from baseline in the total FACT-P score in the docetaxel groups (22 percent in the group given docetaxel every three weeks and 23 percent in the weekly docetaxel group) than in the mitoxantrone group (13 percent). This result suggests that docetaxel has superior palliative effects despite the increase in toxicity. It is likely that the improvement in the quality of life would have been greater if our study had been restricted to symptomatic patients. Overall, the aspects of the quality of life that are assessed by the FACT-P questionnaire were maintained or improved during treatment, with the greatest benefit occurring for prostate-cancer–specific concerns.

Our findings provide evidence that cytotoxic chemotherapy can significantly prolong survival among men with hormone-refractory prostate cancer. Our data suggest that docetaxel plus prednisone is the preferred option for most patients with hormone-refractory prostate cancer.

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