高度医療評価会議　技術委員名簿

氏　名	役　職
飯島（いいじま）　正文（まさふみ）	昭和大学病院　皮膚科　教授
一色（いっしき）　高明（たかあき）	帝京大学医学部附属病院　循環器科　教授
小川（おがわ）　郁（かおる）	慶応義塾大学病院 耳鼻咽喉科学教室 教授
越智（おち）　光夫（みつお）	広島大学病院　整形外科　教授
加藤（かとう）　達夫（たつお）	国立成育医療センター　総長
坂井（さかい）　信幸（のぶゆき）	神戸市立中央市民病院　脳神経外科　部長
澤（さわ）　芳樹（よしき）	大阪大学医学部附属病院 心臓血管呼吸器外科 教授
高橋（たかはし）　政代（まさよ）	理化学研究所 神戸研究所 網膜再生医療研究チームリーダー
田中（たなか）　憲一（けんいち）	新潟大学医歯学総合病院　産婦人科　教授
● 谷川原（たにがわら）　祐介（ゆうすけ）	慶應義塾大学大学院医学研究科生理系専攻薬剤学 教授
● 出口（でぐち）　修宏（のぶひろ）	東松山医師会病院　院長・埼玉医科大学名誉教授
西岡（にしおか）　久寿樹（くすき）	聖マリアンナ医科大学　難病治療研究センター長
本田（ほんだ）　浩（ひろし）	九州大学病院　臨床放射線科　教授
● 松山（まつやま）　晃文（あきふみ）	（財）先端医療振興財団　先端医療センター研究所 膵島肝臓再生研究グループ　グループリーダー
宮澤（みやざわ）　幸久（ゆきひさ）	帝京大学医学部附属病院 中央検査部 臨床病理学 教授

●出席者

資料２－１

新規申請技術の評価結果

整理番号	高度医療名	適応症	承認状況	医薬品・医療機器情報	実施又は調整医療機関	審査担当構成員				総評
						主担当	副担当	副担当	技術委員	
020	再発卵巣癌、原発性腹膜癌、卵巣癌に対する標準化学療法とベバシズマブの併用療法およびベバシズマブ単独の維持療法	上皮性卵巣癌 原発性腹膜癌 卵巣癌	適応外医薬品	・ベバシズマブ（製品名：アバスチン） 中外ロシュ株式会社	埼玉医科大学国際医療センター	柴田	村上	田島		適
021	上皮性卵巣癌・卵管癌・腹膜原発癌に対するパクリタキセル毎週静脈内投与併用カルボプラチン３週毎腹腔内投与	上皮性卵巣癌 原発性腹膜癌 卵巣癌	適応外医薬品	・パクリタキセル （製品名：パクリタキセル注「NK」・パクリタキセル注「サワイ」） 日本化薬株式会社・沢井製薬株式会社 ・カルボプラチン （製品名：パラプラチン注射液・カルボプラチン点滴静注液「サンド」） ブリストル・マイヤーズ株式会社・サンド株式会社	埼玉医科大学国際医療センター	柴田	村上	田島		適
019	高齢者、および、腎機能低下症例に対する血液透析併用バルーン塞栓動脈内抗癌剤投与法（BOAI）、および、放射線照射による集学的膀胱癌治療	75歳以上の高齢者、あるいは腎機能低下を認める浸潤性膀胱癌症例	適応外医薬品 適応外医療機器	・シスプラチン（製品名：ランダ） 日本化薬株式会社 ・中空糸型透析器 （製品名：旭ホローファイバー人工腎臓ＡＰＳ） 旭化成クラレメディカル株式会社	大阪医科大学附属病院	山本	山口	佐藤	出口	条件付き適

資料２－２

高度医療　評価表（番号020　）

評価委員　　主担当：柴田
副担当：村上　　副担当：田島

高度医療の名称	再発卵巣癌、原発性腹膜癌、卵管癌に対する標準化学療法とベバシズマブの併用療法およびベバシズマブ単独の維持療法
申請医療機関の名称	埼玉医科大学国際医療センター
医療技術の概要	現在標準化学療法とされている、パクリタキセル、カルボプラチンにベバシズマブを併用。さらに、維持療法として投与することによって、難治性疾患の予後を改善しようとするものである。また同時に、再発卵巣癌に対する手術適応の意義を明らかにすることも目的としている。

【実施体制の評価】　評価者：村上

１．実施責任医師等の体制	適 ・ 不適
２．実施医療機関の体制	適 ・ 不適
３．医療技術の有用性等	適 ・ 不適
コメント欄：（「不適」とした場合には必ず記載ください。） 再発卵巣癌等に対する化学療法の選択肢が増えるだけでなく予後改善が期待できる。 なお、申請医療機関以外の施設を増やす場合には、医療機関内にベバシズマブの投与経験のある医師が居ることを求める。	
実施条件欄：（修正すれば適としてよいものは、その内容を記載ください。）	

【倫理的観点からの評価】評価者：田島

４．同意に係る手続き、同意文書	適 ・ 不適
５．補償内容	適 ・ 不適
コメント欄：（「不適」とした場合には必ず記載ください。） ○日本語訳付の英語で書かれた説明文書とその補足のための説明・同意文書をセットで患者に交付すること。 ○患者相談等の対応は整備されている（但し、試験責任医師と患者さま対応窓口の欄が総て埋められることが条件）。 （患者相談等の対応が整備されているか、についても記載下さい。）	

実施条件欄：（修正すれば適としてよいものは、その内容を記載ください。）

【プロトコールの評価】　評価者：柴田

６．期待される適応症、効能及び効果	適 ・ 不適
７．予測される安全性情報	適 ・ 不適
８．被験者の適格基準及び選定方法	適 ・ 不適
９．治療計画の内容	適 ・ 不適
１０．有効性及び安全性の評価方法	適 ・ 不適
１１．モニタリング体制及び実施方法	適 ・ 不適
１２．被験者等に対して重大な事態が生じた場合の対処方法	適 ・ 不適
１３．試験に係る記録の取扱い及び管理・保存方法	適 ・ 不適
１４．患者負担の内容	適 ・ 不適
１５．起こりうる利害の衝突及び研究者等の関連組織との関わり	適 ・ 不適
１６．個人情報保護の方法	適 ・ 不適
コメント欄：（「不適」とした場合には必ず記載ください。）	

実施条件欄：（修正すれば適としてよいものは、その内容を記載ください。）

- 申請書 2-2「承認に関する情報」に関して、別の適応で薬剤そのものに対する FDA からの承認はあるものの、再発卵巣癌、原発性腹膜癌、卵管癌といった適応に対する FDA からの承認は無く、米国・欧州・日本とも、薬事上は同様の状況にあるとも言えます(NCCN Drugs & Biologics Compendium には ovarian cancer に関する言及はあるようです)。新たな治療法確立を目指すために国際共同臨床試験に参画することは、本適応に対する開発着手ラグを回避するという面からも意義があると考えます。
- その他、臨床試験実施計画は十分な検討を行った上で作成されていると見受けられますので、特段のコメントはありません。
- 申請書 7-2「予定の試験期間及び症例数」に、50 症例の登録を目標とすると書いてありますが、これは「カルボプラチン＋パクリタキセル併用」群と「カルボプラチン＋パクリタキセル＋ベバシズマブ併用・ベバシズマブ維持療法」群の両方を合算した人数であり、高度医療としては半数の 25 例となるので、混乱を避けるためその旨記載を修正する方が良いと考えます。
- 試験期間は登録 2 年、追跡約 1.5 年と見込まれていますが、ベバシズマブ維持療法期間は患者毎に異なります。すなわち、本試験は試験治療終了後に予後の追跡のみを行う試験と異なることから、高度医療としての実施期間をどこまでと設定するか、制度面での整理が必要ではないでしょうか。

【総評】（主担当の先生が御記載ください。）

総合評価	適　　条件付き適　　継続審議　　不適		
予定症例数	50 例 （標準化学療法群、ベバシズマブ併用・維持療法群の合計として）	予定試験期間	3.5 年間
実施条件：（修正すれば適となる場合は、修正内容を記載ください。）			
コメント欄（不適とした場合は、その理由を必ず記載ください。）			

資料２－３

高度医療　評価表（番号021 ）

評価委員　　主担当：柴田
副担当：村上　　副担当：田島

高度医療の名称	上皮性卵巣癌・卵管癌・腹膜原発癌に対する パクリタキセル毎週静脈内投与併用カルボプラチン３週毎腹腔内投与
申請医療機関の名称	埼玉医科大学国際医療センター
医療技術の概要	パクリタキセル毎週投与を併用したカルボプラチンの静注投与を IP 投与に変更することによって予後が改善されるかどうかを検証する試験。

【実施体制の評価】　評価者：村上

１．実施責任医師等の体制	適 ・ 不適
２．実施医療機関の体制	適 ・ 不適
３．医療技術の有用性等	適 ・ 不適

コメント欄：（「不適」とした場合には必ず記載ください。）

上皮性卵巣癌・卵管癌・腹膜原発癌に対する標準治療の用法・用量変更で予後改善が期待できる。
本申請で計画されている Weekly パクリタキセル静脈内投与とカルボプラチン腹腔内投与の併用療法に関しては、第Ⅲ相試験に移行させる前に第Ⅱ相試験の結果を厳格に評価する必要あり。

実施条件欄：（修正すれば適としてよいものは、その内容を記載ください。）

【倫理的観点からの評価】評価者：田島

4．同意に係る手続き、同意文書	適 ・ 不適
5．補償内容	適 ・ 不適
コメント欄：(「不適」とした場合には必ず記載ください。) ○利益相反について具体的説明が無い。 ○費用負担の説明ぶりが分かりにくい。 ○患者相談等の対応は整備されている（但し、試験責任医師と「患者さま担当」の欄が総て埋められることが条件)。 （患者相談等の対応が整備されているか、についても記載下さい。）	
実施条件欄：(修正すれば適としてよいものは、その内容を記載ください。) ○利益相反について審査が行われることを説明するだけでは不十分で、具体的に利益相反を有する者がいるか否か、いる場合はどのような内容かを記載する。 ○費用負担について、薬剤の無償提供の項目を別途設けて２箇所で説明しているが、両者を１項目に纏め、点滴静脈内投与と腹腔内投与の２つの場合に分けて、それぞれについて費用の内訳を説明する。 →事務局より修正が依頼され、適切に修正されたので４．同意に係る手続き同意文書、についても「適」とする。	

【プロトコールの評価】　評価者：柴田

6．期待される適応症、効能及び効果	適 ・ 不適
7．予測される安全性情報	適 ・ 不適
8．被験者の適格基準及び選定方法	適 ・ 不適
9．治療計画の内容	適 ・ 不適
１０．有効性及び安全性の評価方法	適 ・ 不適
１１．モニタリング体制及び実施方法	適 ・ 不適
１２．被験者等に対して重大な事態が生じた場合の対処方法	適 ・ 不適
１３．試験に係る記録の取扱い及び管理・保存方法	適 ・ 不適
１４．患者負担の内容	適 ・ 不適
１５．起こりうる利害の衝突及び研究者等の関連組織との関わり	適 ・ 不適
１６．個人情報保護の方法	適 ・ 不適
コメント欄：(「不適」とした場合には必ず記載ください。)	
実施条件欄：(修正すれば適としてよいものは、その内容を記載ください。) ・ 期待される適応症、効能及び効果に関して、申請書 2-2「承認に関する情報」に記されている内容をまとめると、	

- カルボプラチン：日本・米・英・独ともに卵巣癌に対する適応が承認されているが腹腔内投与の承認はない。ただし、日本以外の米・英・独では一般臨床で腹腔内投与として用いることに制限はない。
- パクリタキセル：日本・米・蘭・仏・独・伊ともに卵巣癌に対する適応が承認されている。ただし、日本以外の米・蘭・仏・独・伊では一般診療においてweekly投与として用いることに制限はない。

となっており、薬事上の扱いは日本も欧米も同じ状況にあります（すなわち、巷で言われる、海外では承認されているが日本でのみ薬事法の承認を得ていないから薬が使えない･･･は、問題の原因を正しく捉えていない説明であるということです）。このような状況において、日本においてのみ企業に治験実施を求めることは非現実的であると思われるので、本臨床試験によって新しい治療法の根拠が確立するのであれば意義あることと考えます。

・ 第Ⅱ/Ⅲ相試験という臨床試験デザインを選択した経緯は臨床試験実施計画書2.1.6(p14)に記されており問題ないと考えます。ただし、第Ⅱ相部分のfeasibility の解析の方針については、効果安全性評価委員会での審議前に明らかにしておくことが望ましいと考えます（Feasibility の評価にあたって総合的に判断する旨の規定そのものは適切と考えますが、総合的とは言っても想定外に毒性が強かった場合 and/or 想定外に有効性が低かった場合には第Ⅲ相に移行しない、等といった方針は明確に出来るだろうと考えます）。

・ その他、臨床試験実施計画は十分な検討を行った上で作成されていると見受けられますので、特段のコメントはありません。

【総評】（主担当の先生が御記載ください。）

総合評価	適　　条件付き適　　継続審議　　不適		
予定症例数	各群373例（計746例）	予定試験期間	6年
実施条件：（修正すれば適となる場合は、修正内容を記載ください。）			
コメント欄（不適とした場合は、その理由を必ず記載ください。）			

Dr.Colemanセミナー
〈逐次通訳付き〉

卵巣がんについて知っておくべき12のこと
What You Should Know 12 Things
About Ovarian Cancer.

- 共催 -
平成21年度厚生労働科学研究費補助金
NPO法人キャンサーネットジャパン（CNJ）
一般社団法人 北関東婦人科がん臨床試験コンソーシアム（GOTIC）

本日の講師と司会

ロバート・L・コールマン 先生
Robert L. Coleman

M.Dアンダーソンがんセンター婦人科腫瘍学教授
Professor, Department of Gynecologic Oncology
M.D Anderson Cancer Center

藤原 恵一 先生
keiichi Fujiwara

埼玉医科大学国際医療センター婦人科腫瘍科教授
Professor, Department of Gynecologic Oncology
Saitama Medical University International Medical Center

セミナーの進め方

藤原 恵一先生の司会、進行により、12のテーマを取り上げ、それぞれのテーマについてコールマン先生にコメントを頂きます。

- 本日の12のテーマ -

1. 卵巣について
2. 卵巣がんについて
3. 危険因子について
4. 症状について
5. 診断について
6. 病期分類について
7. 治療について
8. 支持療法について
9. 経過観察について
10. 補完代替療法について
11. サポート体制について
12. 臨床試験について

テーマ1：theme 1
卵巣について知っておくべきこと
What You Should Know
About the Ovaries.

テーマ2：theme 2
卵巣がんについて知っておくべきこと
What You Should Know
About the Ovarian Cancer.

テーマ3：theme 3
危険因子について知っておくべきこと
What You Should Know
About the Risk Factors.

テーマ4：theme 4
症状について知っておくべきこと
What You Should Know
About the Symptoms.

テーマ5：theme 5
診断について知っておくべきこと
What You Should Know
About the Diagnosis.

テーマ6：theme 6
病期分類について知っておくべきこと
What You Should Know
About the Staging.

テーマ7：theme 7
治療について知っておくべきこと
What You Should Know
About the Treatment.

1:局所療法（Local Therapy）
2:全身療法（Systemic Therapy）
3:腹腔内療法（Intraperitoneal Therapy）

テーマ8：theme 8
支持療法について知っておくべきこと
What You Should Know
About the Supportive Care.

テーマ9：theme 9
経過観察について知っておくべきこと
What You Should Know
About the Follow-up Care.

テーマ10：theme 10
補完代替療法について知っておくべきこと
What You Should Know
About the Complementary Medicine.

テーマ11：theme 11
サポート体制について知っておくべきこと
What You Should Know
About the Sources of Support.

テーマ12：theme 12
臨床試験について知っておくべきこと
What You Should Know
About the Clinical Trial.

コーヒーブレーク
Coffee Break

Interactive Session
参加者と講師の質疑応答・意見交換

ファシリテーター：NPO法人キャンサーネットジャパン 柳澤 昭浩


ロバート・コールマン先生
M.D Anderson Cancer Center


藤原恵一先生
埼玉医大国際医療センター


ジャクリン・ガノ先生
M.D Anderson Cancer Center


青谷 恵利子 先生
北里大学臨床薬理研究所

トピックス：Topics
1. Differences between US and Japan
米国と日本の違いは？
2. Treatment after recurrence
再発後の治療は？
3. How to cope with cancer
がんとどのように向きあうか？
4. Role of families
家族の役割は？
5. Importance of advocacy
ペイシャントアドボカシーの重要性は？
6. Message to Japanese patients
日本の患者さんへのメッセージ

Thank you for your attention !!
We would like to express our appreciation
on behalf of CNJ and GOTIC
to Rob-san & Jackie-san.

Special Thanks : Ms.Seiko Ushiro

本日の収録の様子は
CNJがん情報ビデオライブラリーで
http://www.cancernet.jp/video/index.html
配信されます。
インターネット環境があれば、
いつでも、どこでも、無償で視聴できます。

平成21年度厚生労働科学研究費補助金/CNJ/GOTIC共催 Dr.Coleman Seminar

Ⅲ. 高度医療実施申請書添付文献

文献 1

Phase III Trial of Carboplatin and Paclitaxel Compared With Cisplatin and Paclitaxel in Patients With Optimally Resected Stage III Ovarian Cancer: A Gynecologic Oncology Group Study

By Robert F. Ozols, Brian N. Bundy, Benjamin E. Greer, Jeffrey M. Fowler, Daniel Clarke-Pearson, Robert A. Burger, Robert S. Mannel, Koen DeGeest, Ellen M. Hartenbach, and Rebecca Baergen

Purpose: **In randomized trials the combination of cisplatin and paclitaxel was superior to cisplatin and cyclophosphamide in advanced-stage epithelial ovarian cancer. Although in nonrandomized trials, carboplatin and paclitaxel was a less toxic and highly active combination regimen, there remained concern regarding its efficacy in patients with small-volume, resected, stage III disease. Thus, we conducted a noninferiority trial of cisplatin and paclitaxel versus carboplatin and paclitaxel in this population.**

Patients and Methods: **Patients with advanced ovarian cancer and no residual mass greater than 1.0 cm after surgery were randomly assigned to receive cisplatin 75 mg/m^2 plus a 24-hour infusion of paclitaxel 135 mg/m^2 (arm I), or carboplatin area under the curve 7.5 intravenously plus paclitaxel 175 mg/m^2 over 3 hours (arm II).**

Results: **Seven hundred ninety-two eligible patients were enrolled onto the study. Prognostic factors were similar in the two treatment groups. Gastrointestinal, renal, and metabolic toxicity, as well as grade 4 leukopenia, were significantly more frequent in arm I. Grade 2 or greater thrombocytopenia was more common in arm II. Neurologic toxicity was similar in both regimens. Median progression-free survival and overall survival were 19.4 and 48.7 months, respectively, for arm I compared with 20.7 and 57.4 months, respectively, for arm II. The relative risk (RR) of progression for the carboplatin plus paclitaxel group was 0.88 (95% confidence interval [CI], 0.75 to 1.03) and the RR of death was 0.84 (95% CI, 0.70 to 1.02).**

Conclusion: **In patients with advanced ovarian cancer, a chemotherapy regimen consisting of carboplatin plus paclitaxel results in less toxicity, is easier to administer, and is not inferior, when compared with cisplatin plus paclitaxel.**

J Clin Oncol 21:3194-3200. ***© 2003 by American Society of Clinical Oncology.***

IN THE United States, standard therapy for women with advanced epithelial ovarian cancer has developed from a series of randomized trials performed primarily by the Gynecologic Oncology Group (GOG). In 1996, this group reported the results of a randomized comparison of cisplatin and cyclophosphamide versus cisplatin and paclitaxel in patients with previously untreated advanced stage III and IV disease.[1] The cisplatin plus paclitaxel regimen was judged superior on the basis of the following results of that trial: an overall improved response rate (73% *v* 60%; $P = .01$); an increased clinical complete response rate (54% *v* 32%); an increase in progression-free survival (PFS; 18.1 *v* 13.6 months; $P < .001$); and, most importantly, an increased overall median survival (38 *v* 24 months; $P < .001$). The results of this study were subsequently confirmed by a European-Canadian trial in patients with stage IIB through IV epithelial ovarian cancer who were similarly randomly assigned to a cisplatin plus cyclophosphamide regimen versus cisplatin plus paclitaxel.[2] In the latter study, cisplatin was combined with paclitaxel administered as a 3-hour infusion, whereas in the GOG trial, paclitaxel was administered as a 24-hour infusion. Furthermore, in the GOG protocol, only suboptimal stage III and IV patients were included (residual masses > 1.0 cm after initial surgery) and there was minimal cross-over to paclitaxel in patients who were initially randomly assigned to receive cisplatin plus cyclophosphamide. Despite these differences in protocol design, both studies demonstrated superiority of initial treatment with cisplatin plus paclitaxel in patients with previously untreated advanced ovarian cancer.

Carboplatin, an analog of cisplatin, has less nonhematologic toxicity than the parent compound. Most randomized trials have reported comparable activity between cisplatin and carboplatin

From Medical Science Department, Fox Chase Cancer Center, Philadelphia, PA; Gynecologic Oncology Group Statistical and Data Center, Roswell Park Cancer Institute, Buffalo; Department of Pathology, New York Presbyterian Hospital-Cornell Medical Center, New York, NY; Division of Gynecologic Oncology, University of Washington School of Medicine, Seattle, WA; Division of Gynecologic Oncology, James Cancer Hospital and Solove Research Institute, Ohio State University, Columbus, OH; Gynecologic Oncology and Obstetrics and Gynecology Departments, Duke University School of Medicine, Durham, NC; Division of Gynecologic Oncology, University of California at Irvine, Orange, CA; Department of Obstetrics and Gynecology, University of Oklahoma Health Sciences Center, Oklahoma City, OK; Department of Obstetrics and Gynecology, Rush Medical Center, Chicago, IL; and Division of Gynecologic Oncology, University of Wisconsin, Madison, WI (affiliate of University of Texas Southwestern Medical Center at Dallas, Dallas, TX).

Submitted February 27, 2003; accepted June 4, 2003.

Supported by National Cancer Institute grants to the Gynecologic Oncology Group Administrative Office (CA 27469) and the Gynecologic Oncology Group Statistical Office (CA 37517).

Address reprint requests to Denise Mackey, Gynecologic Oncology Group, Four Penn Center, 1600 JFK Blvd, Suite 1020, Philadelphia, PA 19103; e-mail: dmackey@gog.org.

0732-183X/03/2117-3194/$20.00

in previously untreated patients with advanced ovarian cancer.[3,4] However, some investigators questioned whether this analog demonstrated equal efficacy in patients with small-volume stage III disease (no tumor nodule > 1.0 cm after initial surgery). An International Ovarian Cancer Consensus Conference in 1993 recommended that carboplatin should not routinely replace cisplatin in patients with potentially curable small-volume stage III disease.[5]

On the basis of these considerations, a phase I study combining carboplatin and paclitaxel was conducted in patients with previously untreated advanced-stage ovarian cancer.[6] Initially, cohorts of patients received paclitaxel at 135 mg/m^2 as a 24-hour infusion, with individual groups of patients receiving carboplatin escalated from an area under the curve (AUC) of 5.0 to 7.5 to 10.0 mg/mL/min. The maximum-tolerated dose was determined to be paclitaxel 135 mg/m^2 in a 24-hour infusion followed by carboplatin at an AUC of 7.5. With multiple cycles of treatment, cumulative granulocytopenia developed and most patients required the addition of colony-stimulating factors (G-CSF) to maintain dose. This phase I study was subsequently amended on the basis of results of a European-Canadian trial that compared 3- *v* 24-hour infusions of paclitaxel.[7] In that trial, patients with recurrent ovarian cancer (previously untreated for recurrence) were randomly assigned in a 2 × 2 factorial trial design to receive either a 3- or 24-hour infusion of paclitaxel at a dose of either 135 or 175 mg/m^2. This trial demonstrated that paclitaxel could safely be administered in a 3-hour schedule with premedication, and that there was significantly less myelosuppression with 3- *v* 24-hour infusion. Furthermore, the efficacy of the 3-hour infusion was comparable to that observed with the 24-hour infusion.[7]

Consequently, in the GOG pilot protocol, additional groups of patients received carboplatin at an AUC of 7.5 in combination with a 3-hour paclitaxel infusion that was escalated from 175 to 225 mg/m^2.[6] In this phase I trial, paclitaxel 175 mg/m^2 over 3 hours followed by carboplatin at an AUC of 7.5 over 30 minutes was identified as the dose and schedule for phase II and phase III trials on the basis of acceptable hematologic toxicity without the need for G-CSF. At this dose level, there were no hospitalizations for febrile neutropenia and no platelet transfusions were required. With the exception of paclitaxel-induced alopecia, there was minimal nonhematologic toxicity reported. Peripheral neuropathy was uncommon and did not exceed grade 2. The most common toxicity was nausea and vomiting, which was easily managed with antiemetics.

The combination of carboplatin plus paclitaxel was found to be an active regimen. In 24 patients with measurable disease, the overall response rate was 75%, including complete responses in 67% of patients. On the basis of the results of the pilot study, GOG Protocol 158 was designed as a noninferiority study to compare the efficacy and toxicity of carboplatin plus paclitaxel with cisplatin plus paclitaxel, which at that time, was the GOG standard treatment regimen for patients with small-volume stage III disease.

PATIENTS AND METHODS

Women with pathologically verified stage III epithelial ovarian cancer (borderline tumors were excluded) underwent a staging laparotomy with cytoreduction. Those who were left with no residual disease greater than 1.0 cm in diameter were eligible for the study. Eligibility criteria also included no previous chemotherapy, a GOG performance status of 0 to 2, WBC at least 3,000/μL, platelets at least 100,000/μL, serum creatinine 2.0 mg/dL or less, and serum bilirubin and AST values of no more than 2 × the institutional upper level of normal. Patients provided written informed consent consistent with all federal, state, and local requirements and must have entered onto the study within 6 weeks of laparotomy. They could not have had previous chemotherapy or radiation for ovarian cancer, nor any previous cancer other than nonmelanoma skin cancer. Pathologic material was centrally reviewed by the GOG Pathology Committee. Each patient case was also reviewed for adequacy of initial surgical procedure, and all of the operative and pathology reports were reviewed to verify eligibility.

On study entry, patients underwent a history, physical examination, and laboratory procedures. Because eligibility disallowed tumor nodules more than 1.0 cm after the initial laparotomy, imaging procedures were not required until completion of six cycles of therapy.

Women in the standard therapy group were to receive cisplatin 75 mg/m^2 intravenously at 1 mg/min and paclitaxel 135 mg/m^2 intravenously as a 24-hour continuous infusion every 3 weeks for a total of six courses. Patients in the experimental group received carboplatin at an AUC of 7.5 mg/mL/min and paclitaxel 175 mg/m^2 as a 3-hour infusion. The carboplatin dose in milligrams was based on the Calvert formula[8]: dose in milligrams = target AUC × [glomerular filtration rate (GFR) + 25]. Creatinine clearance was substituted for GFR and was calculated using the Jelliffe[9] formula on the basis of the patient's weight, age, and serum creatinine level. Premedication consisted of dexamethasone 20 mg orally 12 and 6 hours before the infusion or 20 mg intravenously 30 minutes before the paclitaxel infusion.[10] Both diphenhydramine 50 mg and cimetidine 300 mg were administered intravenously 30 minutes before the paclitaxel infusion.

Adverse effects were graded according to standard GOG toxicity criteria. Patients must have had an absolute neutrophil count ≥ 1,000/μL and platelets more than 100,000/μL before receiving the next course of therapy. Treatment modifications included cycle delay, dose reduction, and the addition of G-CSF (in that sequence). There was no dose modification for uncomplicated nadirs. Patients who required a delay of 2 weeks or less received no dose modification from the previous cycle and G-CSF was not instituted. Those who required a delay of greater than 2 but no more than 3 weeks received modified doses. If patients in the latter group experienced recurrent delays of more than 2 weeks or developed febrile neutropenia during subsequent cycles, G-CSF was added at a dose of 5 μg/kg/d beginning 24 hours after the completion of chemotherapy and continuing for 14 days without further modification to chemotherapy doses. Cycles were not delayed for any gastrointestinal toxicity, grade 1 to 2 peripheral neuropathy, or mild renal toxicity (serum creatinine ≤ 2 mg/dL or creatinine clearance ≥ 50 mL/min). More severe neurologic or renal toxicity that had not resolved before the next scheduled dose necessitated discontinuation of protocol therapy, but follow-up was continued.

At the time of random assignment to treatment arm, the decision to undergo or not undergo second-look laparotomy at the completion of chemotherapy (provided patients met the criteria for surgery) was made. In women who underwent reassessment laparotomy, pathologic response was determined and defined according to one of the following three categories: complete response, partial response with microscopic disease only, or persistent disease.

The GOG Statistical and Data Center randomly assigned the treatment regimen employing a fixed block with an equal number of each regimen after stratification on the amount of residual disease (microscopic or macroscopic) after initial laparotomy and the option of whether a second-look laparotomy was planned after treatment was completed. A sample size of 720 patients was set, with an estimated 3 years (6 years for survival) of follow-up, to observe 382 recurrences (382 deaths for survival) before testing the noninferiority hypothesis: Does carboplatin plus paclitaxel decrease recurrence-

Table 1. Patient Characteristics

Characteristic	Cisplatin + Paclitaxel (n = 400)		Carboplatin + Paclitaxel (n = 392)	
	No. of Patients	%	No. of Patients	%
Age, years				
21-30	2	1	5	1
31-40	28	7	26	7
41-50	101	25	83	21
51-60	109	27	128	33
61-70	117	29	98	25
71-80	38	10	47	12
81-90	5	1	5	1
Ethnicity				
White	353	88	328	84
Black	25	6	25	6
Hispanic	13	3	27	7
Other	9	2	12	3
GOG performance status				
0	182	46	169	43
1	188	47	192	49
2	30	8	31	8
Cell type				
Serous adenocarcinoma	281	70	290	74
Endometrioid adenocarcinoma	45	11	35	9
Mucinous adenocarcinoma	10	3	9	2
Clear-cell carcinoma	10	3	21	5
Other	54	14	37	9
Tumor grade				
1	44	11	35	9
2	139	35	141	36
3	217	54	216	55
Residual disease				
None or microscopic	144	36	137	35
Gross	256	64	255	65
Optional second-look laparotomy				
Yes	201	50	192	49
No	199	50	200	51

Abbreviation: GOG, Gynecologic Oncology Group.

free survival when compared with cisplatin plus paclitaxel in patients with small-volume stage III ovarian cancer? This was a one-sided test with the probability of a type I and type II error both set at .1 for a hazard ratio (carboplatin plus paclitaxel compared with cisplatin plus paclitaxel) of 1.3. These operating characteristics were selected because of the importance of detecting a moderate-sized loss in efficacy with the use of carboplatin plus paclitaxel. A hazard ratio of 1.25 would be detectable with 80% power given the sample size goal.

Overall survival (OS) and PFS were measured from the date of random assignment to treatment. The duration of OS was measured up to the date of death or, for patients still alive, the date of last contact. The duration of PFS was the minimum amount of time until clinical progression, death, or date of last contact. All eligible patients were included in the analysis of OS and PFS (intent-to-treat principle for eligible patients). All causes of death were used to calculate survival, and the estimates of the cumulative proportions of survival were based on Kaplan-Meier procedures.[11] Relative risk (RR) estimates and confidence intervals (CIs) of treatment effects on failure and death while adjusting for prognostic factors was accomplished using the Cox model.[12]

Only eligible women who received at least one course of treatment were included in the assessment of toxicity. The Kruskal-Wallis rank test adjusted for ties was used to test the independence of severity of toxicity (grade 0 to 4) to the assigned treatment.[13]

RESULTS

Eight hundred forty patients entered onto the trial. Forty-eight women, equally distributed between the two treatment groups, were deemed ineligible for the following reasons: wrong stage (14 patients); borderline tumor or not invasive carcinoma (11 patients); inadequate surgery (10 patients); and various pathologic exclusions (eg, wrong cell type) on central pathology review (13 patients). The remaining 792 eligible patients with small-volume stage III disease were randomly assigned to either cisplatin plus paclitaxel or to carboplatin plus paclitaxel. The two groups were balanced for several prognostic factors (Table 1). Slightly more nonwhite (16% *v*

Table 2. Maximum Chemotherapy Cycles Received

Cycle	Cisplatin + Paclitaxel (n = 400)*		Carboplatin + Paclitaxel (n = 392)*	
	No. of Patients	%	No. of Patients	%
1	13	3	11	3
2	8	2	11	3
3	14	4	7	2
4	5	1	11	3
5	17	4	9	2
6	341	85	342	87

*Three patients (two patients from cisplatin + paclitaxel group and one patient from carboplatin + paclitaxel group) did not receive any protocol therapy.

Table 3. Average Dose per Cycle of Chemotherapy

Drug	Cisplatin + Paclitaxel 24-Hour Infusion			Carboplatin + Paclitaxel 3-Hour Infusion		
	Median	10th P	90th P	Median	10th P	90th P
Cisplatin, mg/m^2	74.1	54.7	75.9	—	—	—
Paclitaxel, mg/m^2	133.2	114.2	136.4	174.8	164.5	178.1
Carboplatin, AUC	—	—	—	7.43	5.83	7.65

Abbreviations: AUC, area under the curve; P, percentile.

12%) and patients with serous adenocarcinomas tumors (74% *v* 70%) were randomly assigned to the carboplatin plus paclitaxel group. Sixty-five percent of patients had gross residual disease, whereas the remaining patients had no residual or microscopic disease after the initial laparotomy.

Table 2 summarizes the number of cycles by treatment and Table 3 summarizes the average dose of chemotherapy received per cycle. Eighty-five percent of patients completed six cycles of the cisplatin regimen compared with 87% of those completing the carboplatin regimen. In patients randomly assigned to arm I, the median (average dose per cycle) dose of cisplatin and paclitaxel was 74.1 and 133 mg/m^2, respectively. Among patients randomly assigned to carboplatin and paclitaxel, the median AUC was 7.4 and dose was 175 mg/m^2, respectively.

Grade 3 to 4 adverse effects are listed in Table 4. Patients treated with the cisplatin regimen experienced more (statistically significant) leukopenia, gastrointestinal, renal (genitourinary), and metabolic (hypomagnesemia or abnormal electrolytes) toxicities than did those treated with carboplatin. Patients treated with the carboplatin regimen experienced more (statistically significant) grade 2 to 4 thrombocytopenia and grade 1 to 2 pain. Grade 3 or 4 neutropenia occurred in the majority of women on this trial, but its consequences were manageable, with few patients having documented infection or requiring hospitalization. Regarding thrombocytopenia, there were no reports of clinically significant bleeding or the need for platelet transfusion. Grade 2 to 4 neurologic toxicity (primarily peripheral neuropathy) occurred with similar frequency; 31% in the cisplatin arm and 28% in the carboplatin arm.

Inasmuch as the protocol included only patients with small-volume stage III disease, eligible patients did not have measurable disease. A second-look laparotomy to assess disease status after six cycles of chemotherapy was not mandatory, and surgically confirmed negative second-look frequency was not a statistical end point of this study. However, it was required that the decision regarding whether a patient would undergo second-look laparotomy after six cycles of chemotherapy be made at the time of registration. Three hundred ninety-three (50%) patients elected second-look surgery and results are summarized in Table 5. Of the 325 patients who either underwent surgical restaging or had clinically determined progressive disease before the restaging procedure could be performed, there were 160 (50%) negative second-look laparotomies.

Two hundred eighty-five (73%) patients treated with carboplatin and paclitaxel have experienced a recurrence of disease compared with 303 (76%) treated with cisplatin and paclitaxel. Figure 1 displays PFS, which includes 25 deaths that occurred without prior documented recurrence. Ninety percent of patients have been observed for at least 48 months or have died. Median PFS in the carboplatin group is 20.7 months compared with 19.4 months for the cisplatin group (not significant). The RR of treatment failure is 0.88 (95% CI, 0.75 to 1.03) when comparing carboplatin plus paclitaxel with cisplatin plus paclitaxel. Figure 2 compares the PFS by treatment group stratified by whether the patient had any gross residual disease after surgery. The RR of treatment failure for carboplatin plus paclitaxel to cisplatin plus paclitaxel is 0.89 and 0.85 in patients with gross residual disease and those with microscopic or no residual disease, respectively.

Two hundred seven patients (53%) treated with carboplatin plus paclitaxel have died compared with 230 patients (58%) treated with cisplatin plus paclitaxel. Median survival is 57.4 months for carboplatin plus paclitaxel versus 48.7 months for

Table 4. Grade 3 to 4 Adverse Effects

Adverse Effect	Cisplatin + Paclitaxel (n = 400)				Carboplatin + Paclitaxel (n = 392)			
	Grade 3		Grade 4		Grade 3		Grade 4	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Leukopenia*	205	51	49	12	207	53	23	6
Thrombocytopenia*	11	3	9	2	74	19	80	20
Granulocytopenia	60	15	312	78	67	17	284	72
Gastrointestinal*	55	14	35	9	20	5	19	5
Neurologic	30	8	1	0	26	7	1	0
Alopecia	0	0	0	0	0	0	0	0
Metabolic*	24	6	7	2	6	2	3	1
Genitourinary*	11	3	1	0	3	1	0	0
Pain*†	2	1	1	0	2	1	1	0

*Statistically significant difference at the .05 level.

†Grade 1 to 2 pain: carboplatin + paclitaxel = 101 (26%); cisplatin + paclitaxel = 60 (15%).

Table 5. Second-Look Laparotomy Results

Finding at Second Look	Cisplatin + Paclitaxel		Carboplatin + Paclitaxel	
	No. of Patients	%	No. of Patients	%
Negative second look	77	46	83	53
Positive second look	76	45	58	37
Early clinical progression or death	15	9	16	10
Total with known outcome	168	100	157	100
Results not available				
Refused surgery	28*		31*	
Surgery medically contraindicated	5		4	
Total not available	33		35	

*Overall frequency of refusal is 15%.

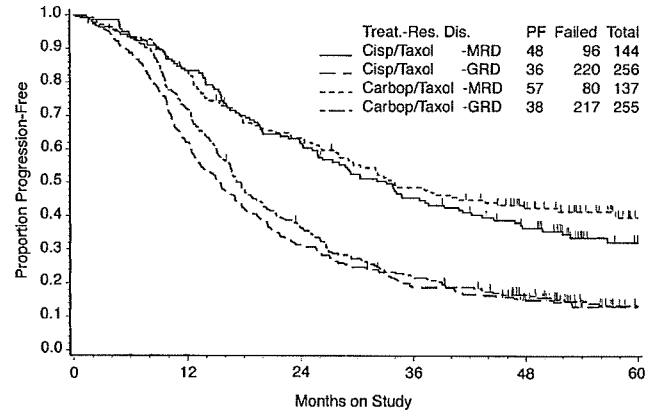

Fig 2. Progression-free survival by treatment group and microscopic (Micro) or gross residual disease (Res. Dis.). Treat., treatment; Carbop, carboplatin; Cisp, cisplatin.

cisplatin plus paclitaxel (Fig 3). The RR is 0.84 (95% CI, 0.70 to 1.02). Figure 4 compares survival between patients with macroscopic residual disease and patients with no (or microscopic) disease by treatment group. The RR estimates for treatment within the residual disease categories are the same.

Figure 5 compares survival from time of recurrence by treatment. Median survival after recurrence is 23 months, and in this exploratory subset analysis there does not appear to be any difference between treatments. Recurrence is associated with a poor prognosis and long-term survival (> 60 months) is infrequent, without any evidence for a plateau.

DISCUSSION

The results of this study demonstrate that the combination of carboplatin plus paclitaxel is not inferior to cisplatin plus paclitaxel with regard to PFS and survival in patients with small-volume stage III epithelial ovarian cancer. The RR of failure is 0.88 (95% CI, 0.75 to 1.03). The RR of death is 0.84 (95% CI, 0.70 to 1.02). This study was designed as a noninferiority trial and the results essentially exclude the possibility that the carboplatin regimen is inferior to the cisplatin regimen. This trial was not designed to determine whether the carboplatin regimen was superior to the cisplatin regimen. Nonetheless, the 16% reduced risk of death is of interest because it is suggestive that carboplatin may provide a slight increase in efficacy over cisplatin. The dose of carboplatin (AUC 7.5) in this trial may result in more platinum exposure than the cisplatin dose (75 mg/m^2). However, previous trials have failed to show a benefit for increasing doses of carboplatin (either as a single agent or in combination with cyclophosphamide).[14,15] It is possible that a pharmacodynamic interaction exists between carboplatin plus paclitaxel, resulting in a better outcome when higher doses of carboplatin are used in combination with paclitaxel.

It is unlikely that a 3-hour infusion of paclitaxel (as used in combination with carboplatin) is superior to a 24-hour infusion (as used in combination with cisplatin) because previous randomized trials have not demonstrated a significant difference in outcomes with different schedules of administration.[7] However, to identify the potential role of carboplatin AUC 7.5 versus any lower dose of carboplatin would require a prospective randomized trial that compares two different doses of carboplatin in combination with the same dose and schedule of paclitaxel.

Two other prospective randomized trials have been performed comparing carboplatin plus paclitaxel versus cisplatin plus paclitaxel in patients with advanced ovarian cancer. In the Danish-Netherlands Trial,[16] there was an insufficient number of patients to determine a statistical equivalency, whereas in the Arbeitsgemeinschaft Gynäkologie trial from Germany,[17] 800 patients with

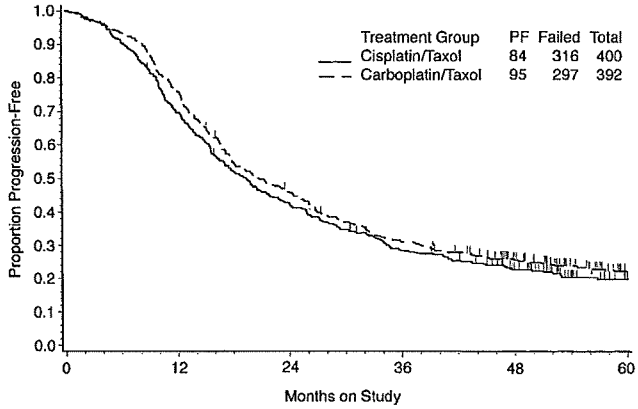

Fig 1. Progression-free survival by treatment group.

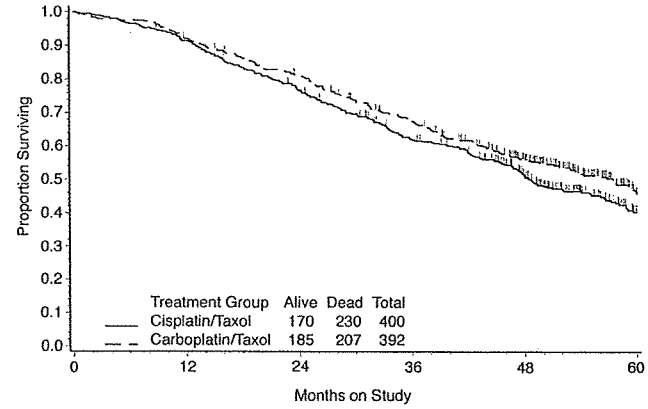

Fig 3. Observed survival by treatment group.

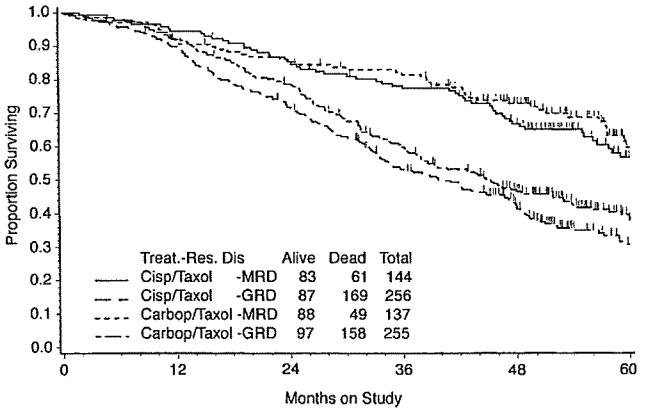

Fig 4. Observed survival by treatment group, and microscopic (Micro) or gross residual disease (Res. Dis.). Treat., treatment; Carbop, carboplatin; Cisp, cisplatin.

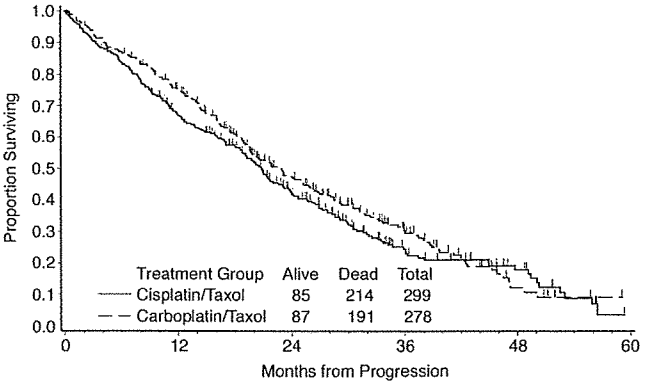

Fig 5. Survival from time of recurrence by treatment group.

advanced-stage ovarian cancer were randomly assigned to similar regimens. Investigators reported no significant difference in PFS and OS between the two treatment groups. However, in the German study, the cisplatin plus paclitaxel regimen used paclitaxel 185 mg/m^2 as a 3-hour infusion instead of 135 mg/m^2 as a 24-hour infusion as used by the GOG in its combination trial with cisplatin. In addition, the carboplatin plus paclitaxel regimen used a slightly lower dose of carboplatin (AUC 6.0 versus 7.5) and a higher dose of 3-hour paclitaxel (185 instead of 175 mg/m^2). Both European trials included patients with stage II to IV disease.

In contrast, GOG Protocol 158 was confined to patients with small-volume stage III disease, and it is within this group of patients that a decrease in efficacy could have the greatest potential influence on survival. The GOG trial fails to support the hypothesis that carboplatin is inferior to cisplatin in patients with small-volume stage III ovarian cancer. Similarly, concerns had been raised regarding the relative efficacy of a 3-hour infusion of paclitaxel versus prolonged infusions[1] on the basis of in vitro toxicity data that demonstrated increased cell kill with prolonged exposure to paclitaxel.[18] The results of this trial, however, failed to support the contention that a 3-hour infusion is less efficacious than a 24-hour infusion of paclitaxel in patients with small-volume stage III ovarian cancer when used in combination with a platinum compound.

The carboplatin plus paclitaxel regimen was also associated with less gastrointestinal and metabolic toxicity (Table 4). The difference in toxicity relates primarily to increased nephrotoxicity caused by cisplatin and to its emetogenic effects. Of note in this study is that there was no difference reported for neurotoxicity at the completion of six cycles of treatment. Both European studies[16,17] have reported less neurotoxicity with the carboplatin plus paclitaxel regimen when compared with cisplatin plus paclitaxel. However, in those studies, cisplatin was combined with a 3-hour infusion of paclitaxel, which is a schedule that shows a high degree of neurotoxicity.[2] Furthermore, the outpatient carboplatin plus paclitaxel regimen is easier to administer than is the cisplatin plus paclitaxel regimen, for which most patients are hospitalized for a 24-hour paclitaxel infusion. On the basis of at least equal activity with regard to PFS and OS, and a more favorable toxicity profile, carboplatin plus paclitaxel is considered the preferred regimen for patients with small-volume stage III ovarian cancer.

Although this study has demonstrated that carboplatin plus paclitaxel is the current treatment of choice for patients with small-volume stage III disease, the results also emphasize the need for more effective therapy. More than 70% of patients have experienced disease recurrence, with a median time to progression of less than 2 years. Median survival after progression is less than 2 years, and median survival from time of diagnosis is between 4 and 5 years. This indicates that treatment after progression, although not curative, may extend survival.

The GOG, in cooperation with investigators from Europe and Asia, is performing a five-arm randomized trial comparing carboplatin plus paclitaxel to new three-drug combinations (carboplatin plus paclitaxel plus gemcitabine, or carboplatin plus paclitaxel plus encapsulated doxorubicin) and sequential doublets (carboplatin and topotecan followed by carboplatin and paclitaxel, or carboplatin and gemcitabine followed by carboplatin and paclitaxel).[19] Until that trial is completed, the standard therapy for ovarian cancer in the GOG continues to be the two-drug combination of carboplatin plus paclitaxel.

APPENDIX

The appendix is included in the full text version of this article only, available on-line at www.jco.org. It is not included in the PDF version.

REFERENCES

1. McGuire WP, Hoskins WJ, Brady MF, et al: Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N Engl J Med 334:1-6, 1996

2. Piccart MJ, Bertelsen K, James K, et al: Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: Three-year results. J Natl Cancer Inst 92:699-708, 2000

3. Aabo K, Adams M, Adnitt P, et al: Chemotherapy in advanced ovarian cancer: Four systematic meta-analyses of individual patient data from 37 randomized trials. Br J Cancer 78:1479-1487, 1998

4. Go RS, Adjei AA: Review of the comparative pharmacology and clinical activity of cisplatin and carboplatin. J Clin Oncol 17:409-422, 1999

5. Vermorken JB, ten Bokkel Huinink WW, Eisenhauer EA, et al: Carboplatin versus cisplatin. Ann Oncol 4:S41-S48, 1993

6. Bookman MA, McGuire WP, Kilpatrick D, et al: Carboplatin and paclitaxel in ovarian carcinoma: A phase I study of the Gynecologic Oncology Group. J Clin Oncol 14:1895-1902, 1996

7. Eisenhauer EA, ten Bokkel Huinink WW, Swenerton KD, et al: European-Canadian randomized trial of paclitaxel in relapsed ovarian cancer: High-dose versus low-dose and long versus short infusion. J Clin Oncol 12:2654-2666, 1994

8. Calvert AH, Newell DR, Gumbrell LA, et al: Carboplatin dosage: Prospective evaluation of a simple formula based on renal function. J Clin Oncol 7:1748-1756, 1989

9. Jelliffe RW: Creatinine clearance: Bedside estimate. Ann Intern Med 79:604-605, 1973

10. Bookman MA, Kloth DD, Kover PE, et al: Short-course intravenous prophylaxis for paclitaxel-related hypersensitivity reactions. Ann Oncol 8:611-614, 1997

11. McGuire WP: Taxol: A new drug with significant activity as a salvage therapy in advanced epithelial ovarian carcinoma. Gynecol Oncol 51:78-85, 1993

12. Cox DR: Regression model and life tables (with discussion). J R Stat Soc B34:187-219, 1972

13. Kruskal WH, Wallis WA: Use of ranks in one-criterion variance analysis. J Am Stat Assoc 47:583-621, 1952

14. Jakobsen A, Bertelson K, Anderson JE, et al: Dose-effect study of carboplatin in ovarian cancer: A Danish Ovarian Cancer Group Study. J Clin Oncol 15:193-198, 1997

15. Gore M, Mainwaring P, A'Hern R, et al: Randomized trial of dose-intensity with single-agent carboplatin in patients with epithelial ovarian cancer. J Clin Oncol 16:2426-2434, 1998

16. Neijt JP, Engelholm SA, Tuxen MK, et al: Exploratory phase III study of paclitaxel and cisplatin versus paclitaxel and carboplatin in advanced ovarian cancer. J Clin Oncol 18:3084-3092, 2000

17. du Bois A, Lück HJ, Meier W, et al: Cisplatin/paclitaxel vs. carboplatin/paclitaxel in ovarian cancer: Update of an Arbeitsgemeinschaft Gynäekologische Onkologie (AGO) Study Group Trial. Proc Am Soc Clin Oncol 18:356a, 1999 (abstr 1374)

18. Liebmann JE, Cook JA, Lipschultz C, et al: Cytotoxic studies of paclitaxel (Taxol) in human tumour cell lines. Br J Cancer 68:1104-1109, 1993

19. Bookman M: Developmental chemotherapy in advanced ovarian cancer: Incorporation of newer cytotoxic agents in a phase III randomized trial of the Gynecologic Oncology Group (GOG-0182). Semin Oncol 29:20-31, 2002