

古澤裕紀 定月みゆき 五味淵秀人 箕浦茂樹	癌の1例				
佐久本 薫	わが国のHIV感染妊娠の現状と母子感染予防	沖縄医報	41	1248-1252	2005
高野政志 喜多恒和	明細胞腺癌に対する手術療法	産科と婦人科	49	593-597	2005
松田秀雄	パルボウイルス感染症	臨床婦人科産科	59	1227-1231	2005
高野政志 喜多恒和 工藤一弥 菊地義公	卵巣癌に対する手術療法の個別化と科学療法	産婦人科治療	90	996-1003	2005
早川 智	免疫学的見地からみた母子感染とその対策	産婦人科治療	90	547-555	2005
早川 智 早川純子 西成田進	抗リン脂質抗体症候群と常位胎盤早期剥離	産婦人科の実際	54	579-584	2005
岡本三四郎 芝崎智子 高野政志 喜多恒和 古谷健一 菊地義公	子宮筋層病変を含む骨盤内腫瘍における針生検の臨床病理学的検討（第2報）	子宮筋層病変生検研究会誌	5	4-5	2005
平川 誠 案座間誠 知花美紀 正本 仁 佐久本薫 金澤浩二 吉田朝秀 安里義秀 太田孝男	胎児水腫を呈した先天性サイトメガロウイルス感染症の1例	日産婦沖縄誌	26	67-71	2005
島袋 史 砂川綾子 銘苅桂子 平川 誠 正本 仁 佐久本薫 金澤浩二	子宮筋腫合併妊娠に発生した深部静脈血栓症の1例	日産婦沖縄誌	27	35-39	2005
砂川綾子 正本 仁 佐久本薫 金澤浩二 城間 肇 金城実男 武島正則	急性虫垂炎合併妊娠の1症例	日産婦沖縄誌	27	58-60	2005
早川 智	源実朝の二日酔い	産科と婦人科	1	98-101	2005
早川 智	ダビデ王の低体温症	産科と婦人科	2	242-245	2005
早川 智	スコットランド王女メアリの拒食症	産科と婦人科	3	391-395	2005
早川 智	女教皇ジョヴァンナの伝説	産科と婦人科	4	500-504	2005
早川 智	平清盛の高熱	産科と婦人科	5	638-641	2005
早川 智	淀の方の更年期障害	産科と婦人科	6	776-780	2005
早川 智	武田信玄と膈の病	産科と婦人科	7	919-923	2005

早川 智	エドワード2世の同性愛	産科と婦人科	9	1204-1207	2005
早川 智	オーストリア皇后エリザベートのスリーサイズ	産科と婦人科	10	1339-1341	2005
早川 智	石田三成の過敏性腸症候群	産科と婦人科	11	1677-1679	2005
早川 智	ジェームズ1世と嫌煙権	産科と婦人科	12	1784-1789	2005
外川正生	HIV母子感染対策（ガイドライン）	小児内科	37	327-331	2005
外川正生	わが国における小児HIV/AIDS診療の現状と問題点	小児科	46	507-514	2005
和田裕一	エイズの母子感染とその対策	産婦人科治療	90	160-163	2005
塚原優己 喜多恒和 和田裕一 外川正生 戸谷良造 稲葉憲之	HIV	産科と婦人科	72	987-993	2005
塚原優己 矢永由里子 稲葉憲之 喜多恒和 稲葉淳一 山田里佳 蓮尾泰之 源河いくみ 外川正生 大金美和 川戸美由紀	HIVと妊娠をめぐる諸問題	日本エイズ学会誌	7	93-98	2005
塚原優己 和田裕一 吉野直人 喜多恒和 稲葉憲之 戸谷良造	わが国における妊婦HIV抗体検査の実施状況 - 以前続く地域格差 -	産婦人科の実際	53	1521-1528	2005
塚原優己	性感染症の最近の動向	産婦人科治療	90	278-285	2005
山田里佳 五味淵秀人 箕浦茂樹	HIV感染者におけるヒトパピローマウイルス（HPV）感染と子宮頸部異常	産婦人科の実際	54	1129-1135	2005
山田里佳	妊婦HIVスクリーニング検査における偽陽性の発生率とその対応	日産婦医会報	8	10-11	2005
稲葉憲之 大島教子 西川正能 和田裕一 喜多恒和 外川正生 塚原優己 戸谷良造	妊婦HIVスクリーニングの実態と問題点	産婦人科の世界	57	1103-1114	2005
稲葉憲之	B型肝炎ウイルス母子感染	栃木県医学会会誌	35	81-85	2005

		予防の見直し				
渡辺 博 稲葉憲之	西川正能	感染症合併妊娠 1) ウイルス性肝炎	産科と婦人科	11	1537-1541	2005
稲葉憲之 西川正能 白木和夫	大島教子 池田綾子	肝炎ウイルスと母子感染 対策 - とくにB, C型肝炎ウ イルスについて -	産婦人科治療	90	617-623	2005
稲葉憲之 西川正能 白木和夫	大島教子 池田綾子	肝炎ウイルス - とくにB, C 型肝炎ウイルスの母子感 染対策について -	産科と婦人科	72	980-985	2005
渡辺 博	稲葉憲之	医療者間、患者とのコミュ ニケーション、チーム医療	日産婦学会誌	57	493-497	2005
白木和夫 稲葉憲之 田尻 仁 松井 陽 戸苅 創 日野茂雄	大戸 斉 藤澤知雄 神埼 晋 森島恒雄 木村昭彦	C型肝炎ウイルスキャリア 妊婦とその出生児の管理 ならびに指導指針	日本小児科学会雑誌	109	78-79	2005
坂本尚徳 稲葉憲之	深澤一雄	子宮癌	獨協医学会	32	189-196	2005

7005006/A (刊行物)

平成17年度 厚生労働科学研究費補助金
エイズ対策研究事業
(H15-エイズ-007)

HIV感染妊婦の早期診断と治療および
母子感染予防に関する臨床的・疫学的研究

平成17年度
刊行物

平成18年3月

主任研究者 稲葉 憲之
(獨協医科大学 大学病院長)

研究成果の刊行に関する一覧表

発表者氏名	論文タイトル名	発表誌名	巻・号	ページ	出版年	
Panichi PB Maggioni A Hacker N, Landoni F Ackermann S Campagnutta E (解説: 喜多恒和)	Systematic aortic and pelvic lymphadenectomy versus resection of bulky nodes only in optimally debulked advanced ovarian cancer: a randomized clinical trial	JCLS	3	91-93	2005	... 7
Kikuchi Y, <u>Kita T</u> <u>Takano M</u> , <u>Kudoh K</u> Yamamoto K	Treatment options in the management of ovarian cancer	Pharmacother	6	743-754	2005	...10
Khew V C, Leah A Fujii K, <u>Kudoh K</u> <u>Kita T</u> , Kikuchi Y Zachariahe S Yick F W, Yong L Wei CS	Application of Expression Genomics for Predicting Treatment Response in Cancer	Ann. N. Y. Acad. Sci	1058	186-195	2005	...22
Xin K-Q, Jounai N Someya K, Honma K Mizuguchi H Naganawa S <u>Kitamura K</u> <u>Hayakawa S</u> Saha S, Takeshita F Okuda , Honda M Klinman DM, Okuda K	Prime-boost vaccination with plasmid DNA and a chimeric adenovirus type 5 vector with type 35 fiber induces protective immunity against HIV	Gene Therapy		1-9	2005	...32
Miura N, Yamamoto M Fukutake M, Ohtake N Iizuka S, Ishige A Sasaki H, Fukuda K Yamamoto T <u>Hayakawa S</u>	Anti-CD3 induces bi-phasic apoptosis in murine intestinal epithelial cells: possible involvement of the Fas/Fas ligand system in different T cell compartments	Int. Immunology	17	513-552	2005	...41
<u>Sakumoto K</u> , Nagai Y Inamine M, Kanazawa K	Primary omental gestational choriocarcinoma	Gynecologic Oncology	97	243-245	2005	...51

	ascertained by deoxyribonucleic acid polymorphism analysis					
<u>Matsuda H</u> Sakaguchi K Shibasaki T Takahashi H Kawakami Y Furuya K, Kikuchi Y	Cerebral edema on MRI in severe preeclamptic women developing eclampsia	J. Perinat. Med.	33	199-205	2005	...54
<u>Matsuda H</u> Kawakami Y Furuya K, Kikuchi Y	Intrauterine therapy for a cytomegalovirus-Infected symptomatic fetus	BJOG	111	756-757	2005	...61
<u>Matsuda H</u> Sakaguchi K Shibasaki T Takahashi H Kawakami Y Furuya K	Intrauterine therapy for parvovirus B19 infected symptomatic fetus using B19 IgG-rich high gammaglobulin	J. Perinat. Med	33	561-563	2005	...63
Ami Y, Izumi Y Matsuo K, Someya K Kanekiyo M Horibata S <u>Yoshino N</u> , Sakai K Shinohara K Matsumoto S Yamada T, Yamazaki S Yamamoto N, Honda M	Priming-Boosting Vaccination with Recombinant Mycobacterium bovis Bacillus Calmette-Guerin And a Nonreplicating Caccinia Virus Recombinant Leads to Long-Lasting and Effective Immunity	J. Virology	79	12871 - 12879	2005	...66
GInkel FW, Jackson RJ <u>Yoshino N</u> Hagiwara Y Metsger DJ Connell TD, Vu HL Martin M Fujihashi K McGhee R	Enterotoxin-Based Mucosal Adjuvants Alter Antigen Trafficking and Induce Inflammatory Responses in the Nasal Tract	Infection and Immunity	73	6892-6902	2005	...75
<u>Hayakawa S</u>	No cancer in cancers: Evolutionary trade-off between	Medical Hypotheses	66	888-897	2006	...86

	successful viviparity and tumor escape from the adaptive immune system					
<u>Hayakawa S</u>	Rembrandt' s Bathsheba, possible lactation mastitis following unsuccessful pregnancy	Medical Hypotheses	in press		2006	... 96
Saito S, Takeda Y Sakai M Nakabayashi M <u>Hayakawa S</u>	The incidence of pre-eclampsia among couples consisting of Japanese women and Caucasian men	J Rep. Immu.	in press		2006	... 99
Miwa N, <u>Hayakawa S</u> Miyazaki S, Myojo S Sasaki Y, Sakai M Takikawa O, Saito S	IDO expression on decidual and peripheral blood dendritic cells and monocytes/macrophages after treatment with CTLA-4 or interferon- γ increase in normal pregnancy but decrease in spontaneous abortion	Molecular Human Reproduction	in press		2006	...105
Inaba F, Kawamata H TeramotoT, <u>Fukasawa I</u> , <u>Inaba N</u> Fujimori T	PTEN and p53 abnormalities are indicative and predictive factors for endometrial carcinoma	Oncology Reports	13	17-24	2005	...111
Zhu K, <u>Fukasawa I</u> Furuno M, Inaba F Yamazaki T, Kamemori T, Kosaka N, <u>Ota Y</u> Hayashi M, Maehama T <u>Inaba N</u>	Inhibitory effects of herbal drugs on the growth of human ovarian cancer cell lines through the induction of apoptosis	Gynecologic Oncology	97	405-409	2005	...119
<u>松田秀雄</u> 川上裕一 古谷健一 菊地義公	サイトメガロウイルス (CMT)感染胎児に対する胎内治療と治療効果判定	産婦人科の実際	53	445-451	2004	...124
<u>谷口晴紀</u>	免疫低下 (HIV感染症) と食事	周産期医学	35	166-169	2005	...131
小早川あかり 長坂康子 浜田亜衣子 榎谷法生	診断に苦慮し治療抵抗性であったHIV合併明細胞腺	日産婦東京地方部会会誌	54	434-438	2005	...135

古澤裕紀 定月みゆき 五味淵秀人 箕浦茂樹	癌の1例					
佐久本 薫	わが国のHIV感染妊娠の現 状と母子感染予防	沖縄医報	41	1248-1252	2005	・・・140
高野政志 喜多恒和	明細胞腺癌に対する手術 療法	産科と婦人科	49	593-597	2005	・・・145
松田秀雄	パルボウイルス感染症	臨床婦人科産科	59	1227-1231	2005	・・・150
高野政志 喜多恒和 工藤一弥 菊地義公	卵巣癌に対する手術療法 の個別化と科学療法	産婦人科治療	90	996-1003	2005	・・・155
早川 智	免疫学的見地からみた母 子感染とその対策	産婦人科治療	90	547-555	2005	・・・163
早川 智 早川純子 西成田進	抗リン脂質抗体症候群と 常位胎盤早期剥離	産婦人科の実際	54	579-584	2005	・・・172
岡本三四郎 芝崎智子 高野政志 喜多恒和 古谷健一 菊地義公	子宮筋層病変を含む骨盤 内腫瘍における針生検の 臨床病理学的検討（第2 報）	子宮筋層病変生検研究 会誌	5	4-5	2005	・・・178
平川 誠 案座間誠 知花美紀 正本 仁 佐久本薫 金澤浩二 吉田朝秀 安里義秀 太田孝男	胎児水腫を呈した先天性 サイトメガロウイルス感 染症の1例	日産婦沖縄誌	26	67-71	2005	・・・180
島袋 史 砂川綾子 銘苺桂子 平川 誠 正本 仁 佐久本薫 金澤浩二	子宮筋腫合併妊娠に発生 した深部静脈血栓症の1例	日産婦沖縄誌	27	35-39	2005	・・・186
砂川綾子 正本 仁 佐久本薫 金澤浩二 城間 肇 金城実男 武島正則	急性虫垂炎合併妊娠の1 症例	日産婦沖縄誌	27	58-60	2005	・・・191
早川 智	源実朝の二日酔い	産科と婦人科	1	98-101	2005	・・・194
早川 智	ダビデ王の低体温症	産科と婦人科	2	242-245	2005	・・・198
早川 智	スコットランド王女メア リの拒食症	産科と婦人科	3	391-395	2005	・・・202
早川 智	女教皇ジョヴァンナの伝 説	産科と婦人科	4	500-504	2005	・・・208
早川 智	平清盛の高熱	産科と婦人科	5	638-641	2005	・・・213
早川 智	淀の方の更年期障害	産科と婦人科	6	776-780	2005	・・・217
早川 智	武田信玄と膈の病	産科と婦人科	7	919-923	2005	・・・222

早川 智	エドワード2世の同性愛	産科と婦人科	9	1204-1207	2005	・・・227
早川 智	オーストリア皇后エリザベートのスリーサイズ	産科と婦人科	10	1339-1341	2005	・・・231
早川 智	石田三成の過敏性腸症候群	産科と婦人科	11	1677-1679	2005	・・・235
早川 智	ジェームズ1世と嫌煙権	産科と婦人科	12	1784-1789	2005	・・・239
外川正生	HIV母子感染対策（ガイドライン）	小児内科	37	327-331	2005	・・・245
外川正生	わが国における小児HIV/AIDS診療の現状と問題点	小児科	46	507-514	2005	・・・250
和田裕一	エイズの母子感染とその対策	産婦人科治療	90	160-163	2005	・・・258
塚原優己 喜多恒和 和田裕一 外川正生 戸谷良造 稲葉憲之	HIV	産科と婦人科	72	987-993	2005	・・・262
塚原優己 矢永由里子 稲葉憲之 喜多恒和 稲葉淳一 山田里佳 蓮尾泰之 源河いくみ 外川正生 大金美和 川戸美由紀	HIVと妊娠をめぐる諸問題	日本エイズ学会誌	7	93-98	2005	・・・269
塚原優己 和田裕一 吉野直人 喜多恒和 稲葉憲之 戸谷良造	わが国における妊婦HIV抗体検査の実施状況 - 以前続く地域格差 -	産婦人科の実際	53	1521-1528	2005	・・・275
塚原優己	性感染症の最近の動向	産婦人科治療	90	278-285	2005	・・・283
山田里佳 五味淵秀人 箕浦茂樹	HIV感染者におけるヒトパピローマウイルス（HPV）感染と子宮頸部異常	産婦人科の実際	54	1129-1135	2005	・・・291
山田里佳	妊婦HIVスクリーニング検査における偽陽性の発生率とその対応	日産婦医会報	8	10-11	2005	・・・298
稲葉憲之 大島教子 西川正能 和田裕一 喜多恒和 外川正生 塚原優己 戸谷良造	妊婦HIVスクリーニングの実態と問題点	産婦人科の世界	57	1103-1114	2005	・・・300
稲葉憲之	B型肝炎ウイルス母子感染	栃木県医学会会誌	35	81-85	2005	・・・312

		予防の見直し				
渡辺 博 西川正能 稲葉憲之		感染症合併妊娠 1) ウイルス性肝炎	産科と婦人科	11	1537-1541	2005 ……317
稲葉憲之 大島教子 西川正能 池田綾子 白木和夫		肝炎ウイルスと母子感染 対策 - とくにB, C型肝炎ウ イルスについて -	産婦人科治療	90	617-623	2005 ……322
稲葉憲之 大島教子 西川正能 池田綾子 白木和夫		肝炎ウイルス - とくにB, C 型肝炎ウイルスの母子感 染対策について -	産科と婦人科	72	980-985	2005 ……329
渡辺 博 稲葉憲之		医療者間、患者とのコミュ ニケーション、チーム医療	日産婦学会誌	57	493-497	2005 ……335
白木和夫 大戸 斉 稲葉憲之 藤澤知雄 田尻 仁 神崎 晋 松井 陽 森島恒雄 戸莉 創 木村昭彦 日野茂雄		C型肝炎ウイルスキャリア 妊婦とその出生児の管理 ならびに指導指針	日本小児科学会雑誌	109	78-79	2005 ……340
坂本尚徳 深澤一雄 稲葉憲之		子宮癌	獨協医学会	32	189-196	2005 ……342

Systematic aortic and pelvic lymphadenectomy versus resection of bulky nodes only in optimally debulked advanced ovarian cancer: a randomized clinical trial.

Panici PB, Maggioni A, Hacker N, Landoni F, Ackermann S, Campagnutta E, et al.
J Natl Cancer Inst. 2005; 97: 560-6. PMID: 15840878.

初回腫瘍縮小手術で残存腫瘍径を1cm以下にできた進行上皮性卵巣癌を、骨盤および傍大動脈リンパ節郭清群と腫大リンパ節摘出群とに術中無作為化し、無増悪生存率および全生存率を比較した論文

解説：喜多恒和（防衛医科大学校病院産婦人科講師）

試験の背景

上皮性卵巣癌の欧米諸国での罹患患者数は第5位、臓器別死亡者数は第4位で、米国では2004年に25,000人が罹患し、16,000人が死亡している。その5年生存率は30%程度である。最近のメタアナリシスにより、Ⅲ・Ⅳ期卵巣癌において、徹底的な腫瘍縮小手術は予後を改善する最も重要な因子の1つであることがわかった¹⁾。しかし50~80%の進行卵巣癌において後腹膜リンパ節転移が認められるにもかかわらず、後腹膜リンパ節郭清の治療的意義は、後方視的解析ではその有用性が報告されているものの²⁾、前方視的無作為化臨床試験はこれまで行われてい

なかった。そこで進行卵巣癌において腹腔内病変の摘出がoptimal（残存腫瘍径1cm以下）にできた場合に、骨盤および傍大動脈リンパ節郭清を追加することで予後を改善しうるのか、多施設共同無作為化臨床試験が行われた。

論文の概要

試験期間は1991年から2003年。対象はⅢb・Ⅲc期および胸水中悪性細胞陽性のみのⅣ期上皮性卵巣癌患者427例で、初回手術でoptimalとなった場合、術中に腫大リンパ節摘出群と骨盤および傍大動脈の系統的リンパ節郭清群とに無作為化を行った（表1）。リンパ節摘出群においても1cm径以上

のリンパ節はすべて摘出されたが、摘出数は平均4個のみで、系統的リンパ節郭清群では25個以上の骨盤リンパ節と15個以上の傍大動脈リンパ節が郭清基準とされ、摘出合計の平均は51個であった。術後プラチナ製剤を含む化学療法が行われたが、タキサン製剤との併用は39%のみであった。

再発部位は後腹膜も含め両群に差はなかったが、再発率はそれぞれ69.2%と62.5%、無増悪生存率（PFS）はそれぞれ22.4ヵ月と29.4ヵ月で両群間に有意差を認めた。しかし全生存率（OS）は、それぞれ56.3ヵ月と58.7ヵ月で差がなかった。系統的リンパ節郭清の有無、腫瘍の分化度および残存腫

瘍径の有無を予後因子として多変量解析を行った場合でも、系統的リンパ節郭清はPFSを改善するものの、OSには影響せず、残存腫瘍の有無はPFSとOSの双方に強く影響した。(表2)。ただし系統的リンパ節郭清群においては、リンパ節転移は有意な予後因子であった。

解説

筆者らは、これまでの後方視的な解析による報告と比べて、系統的リンパ節郭清ができる症例は、もとより予後良好である場合が多いというようなバイアスは本臨床試験では排除されているにもかかわらず、系統的リンパ節郭清によりPFSが25% (HR = 0.75) と大きく改善されたことを強調している。また重要な予後因子であるとすでに報告されているリンパ節転移は、腫大リンパ節のサイズとはそれほど関与しないことから、微小転移リンパ節の系統的郭清そのものが予後に影響するであろうと想定される。しかし系統的リンパ節郭清がOSを改善しなかった理由として、筆者らは68.4ヵ月のフォローアップ期間の短さと再発後の再摘出術の有無やセカンドライン化学療法の違いをあげている。しかしフォローアップ期間の延長により系統的リンパ節郭清の意義を再検討できるとは考えがたく、また再発後の治療内容はまったく検討されておらず、一般に両群間にバイアスがかかるとは考えにくい。

初回手術後の残存腫瘍径は、従来より重要な予後因子として確立されており、たとえ1cm径以下の転移リンパ節であってもリンパ節摘出群の残存腫瘍径は郭清群より大きいはずであるか

FIGO 進行期 (n=216)				
年齢中央値	56		59	
FIGO進行期				
IIIb	37	17.5	41	19.0
IIIc	162	76.8	166	76.9
IV	12	5.7	9	4.2
残存腫瘍径				
0	79	37.4	80	37.0
1cm以下	118	55.9	130	60.2
1~2cm	12	5.7	4	1.9
分化度				
1~2	48	22.7	69	31.9
3	160	75.8	142	65.7
組織型				
漿液性	132	62.6	155	71.8
類内臓	28	13.3	21	9.6
粘液性	6	2.8	4	1.9
明細胞	12	5.7	4	1.9
未分化	23	10.9	18	8.3

表1 治療群別の患者背景

FIGO : International Federation of Gynecology and Obstetrics (世界産婦人科連合)。

治療群	PFS		OS	
	HR	P	HR	P
リンパ節摘出群	1.0	0.01	1.0	0.85
系統的リンパ節郭清群	0.75		0.97	
分化度				
1~2	1.0	0.76	1.0	0.25
3	1.04		1.02	
残存腫瘍				
なし	1.0	<0.001	1.0	0.002
あり	1.65		1.59	

表2 無増悪生存率 (PFS) および全生存率 (OS) における多変量解析

ら、PFSに差が出ることは容易に予測できる。しかし筆者らも指摘しているように、多くの患者の再発までには術

後化学療法を終了後6ヵ月以上が経過しており、再発後の化学療法に対する感受性は両群ともに期待されることか

ら、再発後の生存期間が長いことが予測され、全生存期間の差が相殺されてしまった可能性がある。また表1に示したように、残存腫瘍径が1~2cmの症例も解析に含まれており、併せて分化度3および組織型においては、粘液性・明細胞・未分化癌の占める割合は、わずかずつであるがリンパ節摘出群に多く、これらの差の重なりがPFS

に影響しているかもしれない。

系統的リンパ節郭清の真の意義を説明するには、確立された他の予後因子を、例えば漿液性癌で分化度2以下、さらに残存腫瘍なし、のように一定化したうえで、系統的リンパ節郭清の有無を無作為化して解析することが必要であろう。

文献

- 1) Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Monz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during platinum era: a meta-analysis. J Clin Oncol 2002; 20: 1248-59.
- 2) Scarabelli C, Gallo A, Zarrelli A, Visentin C, Campagnutta E. Systematic pelvic and para-aortic lymphadenectomy during cytoreductive surgery in advanced ovarian cancer. Potential benefit on survival. Gynecol Oncol 1995; 56: 328-37.

「信頼」と「実績」の極み
ステッドマン医学辞典シリーズ

総監修 高久 史彦 自治医科大学学長

ステッドマン医学大辞典

改訂第5版【英和・和英】カラー版

全収録語 105,000語/和英索引 90,000語 ← 完璧な和英辞典としても活用できる!

●定価 14,700円 A5判・総頁2,720頁・上製本・ソフトカバー・函入

CD-ROM ステッドマン医学大辞典

改訂第5版【英和・和英】 発音音声、カラーイラストも収録!

●for Windows/for Macintosh 定価 各24,150円

PDA版 ステッドマン医学大辞典
for Palm OS & Pocket PC

改訂第5版【英和・和英】

携帯に便利なPDAで、いつでも、どこでも検索可能!

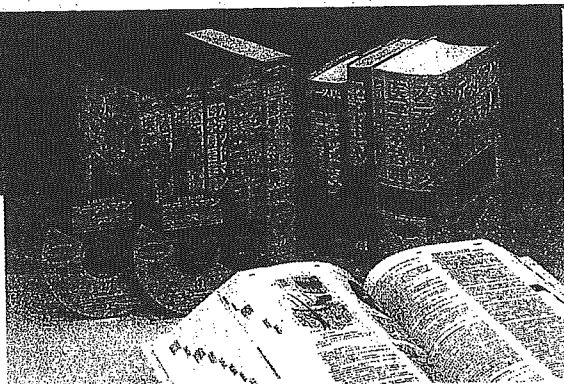
●定価 15,750円 ※イラストや発音音声は収録していません
PDAインストール用データ収録CD-ROM1枚+A5判ユーザーズガイド

CD-ROM ステッドマン医学大辞典
プラス
医学略語辞典 for Windows

改訂第5版【英和・和英】

「ステッドマン医学大辞典」と「ステッドマン医学略語辞典」をセットで1枚のCD-ROMに収録!

●定価 31,500円 CD-ROM1枚+A5判ユーザーズガイド



ステッドマン医学略語辞典

わが国最大の収録略語数 45,000語 最新略語も網羅

●定価 6,825円 A5判・640頁・上製本

CD-ROM ステッドマン医学略語辞典

Win & Macハイブリッド

CD-ROMステッドマン医学大辞典(第5版)に組み込み可能!

●定価 12,600円
CD-ROM1枚+ユーザーズガイドA5判・116頁

ナース版 ステッドマン医学辞典

改訂第2版【英和・和英】

全収録語 41,000語/和英索引 36,000語
解剖図のカラーイラスト27点(カラー別丁32頁)
イラスト・写真170点

●定価 6,300円 B6判・総頁1,568頁・上製本・ソフトカバー

※定価は5%税込み価格です。

M メジカルビュー社

〒162-0845 東京都新宿区西谷本町2番80号 TEL: 03(5228)2050 FAX: 03(5228)2059
URL: <http://www.medicalview.co.jp> E-mail(営業部): eiyo@medicalview.co.jp

Expert Opinion

1. Introduction
2. Induction chemotherapy (primary chemotherapy)
3. Second-line chemotherapy (salvage, consolidation, maintenance chemotherapy)
4. Neoadjuvant chemotherapy
5. Metronomic chemotherapy
6. Molecular-targeted chemotherapy
7. Conclusion
8. Expert opinion

Ashley Publications
www.ashley-pub.com



Treatment options in the management of ovarian cancer

Yoshihiro Kikuchi[†], Tsunekazu Kita, Masashi Takano, Kazuya Kudoh & Kenji Yamamoto

[†]Department of Obstetrics and Gynecology, National Defence Medical College, Tokorozawa, Saitama, Japan

The standard regimen used as primary chemotherapy of ovarian cancer is combination chemotherapy using paclitaxel and carboplatin. The main objective of first-line chemotherapy is to induce complete response. Although most cases respond to the initial chemotherapy, many cases relapse within 3 years. Such relapsed and persistent cases become resistant to first-line chemotherapy and require second-line chemotherapy. Objectives of such a second-line chemotherapy are to obtain disease palliation to cease disease progression. Meanwhile, consolidation or maintenance chemotherapy may be added to prevent or inhibit disease relapse for patients with advanced disease after induction of complete remission by a primary chemotherapy. When the unresectable tumour is presumed by primary surgery, neoadjuvant chemotherapy may be selected. Recently, conventional cytotoxic anticancer drugs containing paclitaxel have been shown to be capable of inhibiting angiogenesis. The notion of 'redefining' chemotherapeutic drugs has been recognised; thus, continuous low-dose chemotherapy – so-called metronomic chemotherapy – has been approved as a new concept. Many new molecular-targeted therapies became available for clinical cancer therapy. The explosion of new molecular targets and the development and application of many powerful technologies should accelerate the discovery of innovative molecular therapeutics. Understanding the molecular mechanisms will help to clarify the pathways in ovarian cancer development and help to identify new therapeutic and diagnostic targets. These are exciting times for new drug development and the treatment of cancer. Cautious optimism should prevail for all investigators involved in translating these exciting new biological findings into new pharmacological agents for treatment of cancer.

Keywords: chemotherapy, ovarian cancer

Expert Opin. Pharmacother. (2005) 6(5):743-754

1. Introduction

For centuries, surgery was considered the only curative treatment for cancer. Likewise, radiation therapy offered some patients a possible cure for localised cancers. However, once the disease had spread from its original site of origin, the patient was deemed inoperable and, therefore, incurable. The first drug used for cancer treatment was a derivative of mustard gas [1]. In 1948, Farber and associates [2] reported on the use of folate antagonists for the treatment of childhood leukaemia. Since that time, > 100 pharmacological agents have been introduced for that treatment of cancer. Combining agents with different mechanisms of action and nonoverlapping toxicities is now considered the most acceptable approach to the eradication of disseminated cancers.

Ovarian cancer is the fifth leading cause of cancer death in women in the US, with an estimated 23,300 cases diagnosed and 13,900 deaths in 2002 [3]. Improvements in the management of ovarian cancer have resulted in increased 5-year

survival rates to > 50% over the period of 1992 – 1997 [3]. Data from Europe have demonstrated increases in 5-year survival that vary from 26% for Eastern Europe to 42% for Northern Europe [4]. However, the prognosis for patients with ovarian cancer remains poor. Up to 75% of patients are diagnosed in the advanced stage and many require chemotherapy after cytoreductive surgery [5]. Although 10 – 15% of patients maintain a response to standard first-line cisplatin/paclitaxel chemotherapy, most patients eventually relapse [6]. The goals of treating advanced recurrent ovarian cancer are mainly palliative, attempting to prolong life and control disease-related symptoms, while minimising treatment-related toxicities and maximising health-related quality of life.

Some significant advances in clinical oncology using standard- or high-dose regimens have been achieved, but such gains seem to have reached a plateau over the past two decades, in part as a result of drug resistance. The shift to alternative targets within the tumour and the use of these targets for the subset of patients who, either because of intrinsic or acquired resistance, are not likely to respond to standard therapy holds promise. The results of Colleoni *et al.* [7] may herald a gradual shift from standard maximum tolerated dose (MTD) or high-dose chemotherapy, to, at least in the chemoresistant population, induction of antiangiogenesis by low-dose chemotherapy. At present, most of the new receptor blocking agents such as gefitinib (ZD-1839/Iressa®, AstraZeneca Pharmaceuticals LP) or cetuximab (C-225/Erbitux™, ImClone Systems Incorporated), as well as antiangiogenic drug (e.g., bevacizumab/Avastin™ [Genentech, Inc.]: the humanised monoclonal antibody to vascular endothelial growth factor [VEGF]), are used with standard chemotherapy regimens, which negates their superior safety profiles. As the cancer patient population ages, should these combinations also be evaluated in the setting of low-dose, frequent, continuous chemotherapy? The time may come when the term 'side effect' for chemotherapeutic drugs not only loses its negative connotations, but takes on a new, and positive, meaning.

2. Induction chemotherapy (primary chemotherapy)

Surgery followed by systemic chemotherapy is the current standard treatment modality for epithelial ovarian cancer, particularly when diagnosis is made at an advanced stage [8,9]. The combination of paclitaxel and cisplatin replaced schemes without paclitaxel after it was shown in the Gynecologic Oncology Group Trial 111 [10] and in a subsequent confirmatory trial [11] that it was more effective than the combination of cyclophosphamide and cisplatin. In fact, paclitaxel combined with carboplatin is considered the standard first-line chemotherapy regimen worldwide because of its more favourable toxicity profile as compared with paclitaxel and cisplatin [12-14]. Surgery and first-line systemic chemotherapy induce complete and partial response in ≤ 80% of patients, with a pathological complete remission rate of ~ 25% [10,11]. Unfortunately, recurrences

occur in the majority of patients, and only 20 – 40% survive after a 5-year follow-up period, with survival being substantially dependant on the initial International Federation of Gynecology and Obstetrics stage [15].

Important questions about the clinical value of platinum/taxane combinations have been raised by the results of the large International Collaborative Ovarian Neoplasm Group 3 study involving 2074 ovarian cancer patients. The data from this trial suggest that there was no benefit, in terms of either progression-free or overall survival, from the use of paclitaxel/carboplatin compared with carboplatin alone or cyclophosphamide/doxorubicin/cisplatin [16]. Furthermore, the incidences of alopecia, fever and sensory neuropathy were significantly higher in the taxane treatment arm compared with carboplatin alone. The SCOTROC Randomised trial in Ovarian Cancer has compared the use of two different taxane preparations in combination with platinum to determine whether there were any differences in efficacy or tolerability. A total of 1077 patients were randomised to receive either docetaxel/carboplatin or paclitaxel/carboplatin [17]. The results indicate that there was no significant difference between these regimens in terms of either median progression-free survival (15.1 months for docetaxel/carboplatin versus 15.4 months for paclitaxel/carboplatin) or overall survival at 18 months (73.5 versus 76.6%, respectively). However, there were some differences between the two treatment groups regarding their tolerability profiles, with paclitaxel associated with significantly greater neurotoxicity, arthralgia/myalgia and weakness in the legs or arms compared with docetaxel. Nevertheless, global quality of life parameters based on the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire were comparable in both treatment arms. These data suggest that individual patients might benefit from the use of one or the other taxane, depending on their predisposition to adverse effects such as neuropathy.

Recent studies assessing the effects of the addition of epirubicin to platinum/taxane have shown a higher response rate among patients in the epirubicin treatment arm compared with those receiving platinum/taxane alone, although there was also a higher incidence of toxicity in these patients [18]. A number of newer chemotherapeutic agents are being assessed for a potential role in first-line treatment regimens for ovarian cancer, including gemcitabine, pegylated liposomal doxorubicin, irinotecan, oxaliplatin and topotecan. Of these agents, topotecan has been extensively studied using a variety of different treatment strategies. The mechanism of action of topotecan (inhibition of topoisomerase I) is different from that of paclitaxel, with no overlap, and synergy has been demonstrated in *in vitro* tumour models with paclitaxel and platinum [19,20]. Topotecan has also shown activity in platinum- and paclitaxel-resistant tumours, and there is an absence of cross-resistance with paclitaxel [21]. Likewise, in Japan, irinotecan (but not topotecan) is frequently used for platinum- and paclitaxel-resistant tumours. Both clear cell carcinoma and mucinous cystadenocarcinoma in advanced stages are poorly responsive

to platinum- or taxane-based chemotherapy [22-24]. In addition, the authors of this review have examined response rates to standard regimens according to histological type. The response rate of clear cell carcinoma was significantly lower (showing 11.1%), compared with 72.5% of serous cystadenocarcinoma [22]. In patients with > 2 cm residual tumour the response rate to cyclophosphamide/adriamycin/cisplatin (CAP) regimen was also lower in mucinous cystadenocarcinoma and clear cell carcinoma compared with serous cystadenocarcinoma and endometrioid adenocarcinoma. However, when etoposide/cisplatin and irinotecan/cisplatin were used to treat mucinous cystadenocarcinoma and clear cell adenocarcinoma, respectively, significant response rates (33 and 50%, respectively) were obtained [25]. The standard regimen for clear cell adenocarcinoma and/or mucinous adenocarcinoma should be evaluated by independent trials. Thus, this group are using a standard regimen (paclitaxel/carboplatin) to treat serous cystadenocarcinoma and endometrioid adenocarcinoma as a first-line chemotherapy, whereas combination chemotherapy using etoposide and cisplatin to treat mucinous cystadenocarcinoma, and combination of irinotecan and cisplatin to treat clear cell carcinoma are used as a first-line chemotherapy.

3. Second-line chemotherapy (salvage, consolidation, maintenance chemotherapy)

Aggressive surgical cytoreduction followed by six cycles of carboplatin plus paclitaxel represents the standard of care for ovarian cancer, from stage 1C to IV [8,9,12-14]. Despite the high response rate reported with this strategy, most (50 – 75%) of the patients who have a complete response relapse ultimately die of ovarian cancer [15,26].

Several types of consolidation treatments have been tested, such as radiotherapy [27,28], hormonal therapy [29] and immunotherapy [30,31]. Most of these studies had small sample size and insufficient power; all of them produced negative results. Recently, two studies have been reported on the use of systemic chemotherapy as consolidation treatment with paclitaxel and epirubicin [32,33]. Markman *et al.* [32] showed that 12 cycles of single-agent paclitaxel, compared with 3 cycles of the same drug, significantly prolonged progression-free survival in patients with clinical complete response to first-line carboplatin and paclitaxel. This study was discontinued early after an interim analysis showed a statistically significant improvement in time to progression, with a 7-month advantage for the arm receiving 12 cycles compared with that receiving 3 cycles. This is the first randomised study that has suggested that maintenance chemotherapy may impact survival. In addition, it has been reported that chronic administration of single weekly paclitaxel in heavily pretreated ovarian cancer patients could be safely used and resulted in long progression-free interval [34].

Another trial with negative results has been reported in abstract form by Scarfone *et al.* [33], comparing four cycles of epirubicin (120 mg/m²) with no treatment in the same setting

of patients. Preliminary results (presented at the 2002 Annual Meeting of the American Society of Clinical Oncology) indicate that there was no advantage in time to progression for patients treated with epirubicin. The addition of epirubicin to the standard carboplatin and paclitaxel treatment did not improve progression-free survival [35,36].

Improvements in ovarian cancer management mean that it may now be a long-term disease for which treatment must be carefully considered. Optimal sequencing of chemotherapy may help to enhance patient's benefit of therapy and minimise toxicity. The response to retreatment with platinum or a platinum/taxane combination is strongly influenced by the treatment-free interval after initial therapy with a platinum combination. Response rates to platinum retreatment in platinum-resistant patients (relapse within 6 months) are lower than those in platinum-sensitive patients (relapse after 6 months). It is possible that if one was able to extend the interval until relapse, response rate to platinum may be improved. Therefore, increasing the platinum-free interval by using non-platinum-based chemotherapy for treatment after relapse appears to increase the response to later rechallenge with platinum [37]. Many alternative agents have been investigated for the treatment of patients with relapsed ovarian cancer. For the selection of the optimal chemotherapy regimen at first relapse, patients are usually characterised according to their degree of sensitivity or resistance to the treatment, depending on the interval between initial response and first relapse (< 3 months: refractory; < 6 months: resistance; 6 – 12 months: sensitive; 12 – 24 months: very sensitive) [37]. In addition to treatment-free interval, prediction of response includes a number of prior regimens, toxicity from prior therapy, previous use of growth factors and/or transfusions, performance status, volume of disease, number of disease site, ascites, and signs and symptoms of gastrointestinal dysfunction. At present, complete responses to treatment for recurrent disease are rare, particularly if the patient's time to relapse is short. Treatment-free intervals decrease after each relapse and retreatment, which may increase toxicities. The median survival after disease recurrence is in the range of 12 – 24 months [36]. As a general rule, the later the recurrence, the better the prognosis for survival duration. The aims of palliative treatment in relapsed ovarian cancer are, therefore, to control disease-related symptoms and minimise the side effects of treatment in order to prolong survival and delay time to progression. Maintenance or, preferably, improvement in quality of life becomes an important goal in these patients. A number of different strategies may be employed in the management of patients with relapsed ovarian cancer, including retreatment with platinum or salvage therapy with a variety of other agents, either alone or in combination regimens.

One treatment management option in relapsed patients is to reuse a platinum/taxane combination. However, response rates to such therapy are particularly low in patients with a short treatment-free interval. The correlation between platinum-free interval and response to second-line platinum

Table 1. Comparison of survival between adjuvant chemotherapy after initial debulking surgery and neoadjuvant chemotherapy followed by interval surgery.

	Comparison of survival	Comparison of debulking
Jacob (1991) [68]	Median survival	Optimal (%)
Adjuvant	18 months	39%
NAC therapy	16 months	77% (p = 0.02)
Onnis (1996) [70]	3- and 5-year survival	Optimal (%)
Adjuvant	31 versus 21%	29%
NAC therapy	27 versus 19%	42%
Schwartz (1999) [71]	Median survival	
Adjuvant	2.18 years	
NAC therapy	1.07 years	
Vergote (1998) [72]	3-year survival	
Adjuvant	26%	
NAC therapy	42% (p = 0.001)	

NAC: Neoadjuvant chemotherapy.

combination therapy has been clearly demonstrated in number of studies [37-39]. The number of responders in the 6- to 12-months category is thought to be in the 25 – 30% range, slowly increasing to a rate of 60 – 70% at 2 years. Combinations of carboplatin and paclitaxel appear to have a higher response rate and may also blunt the platinum-free interval effect seen with single-agent platinum treatment [40]. This was also the result of the recently presented International Collaborative Ovarian Neoplasm 4 report [41]. The platinum-free interval has been used to classify relapsed patients for therapy. Essentially all agents appear to be more active in patients off therapy for > 6 months. Because all of these patients are currently incurable, the overall goal of therapy is to extend survival through a series of chronic treatments. The most beneficial sequence of treatments for particular patients has not been established.

A considerable number of nonplatinum agents have been investigated for the treatment of patients with relapsed ovarian cancer. Examples of efficacy with single-agent therapy with paclitaxel, topotecan (because topotecan is not approved in Japan, irinotecan is used), liposomal doxorubicin, etoposide and gemcitabine in recurrent ovarian cancer, as well as their known cumulative toxicities, have been shown [39-41,44-56].

Paclitaxel, a unique antimicrotubule agent, has been one of the most promising drugs to enter into clinical trials in the setting of cisplatin-refractory ovarian cancer. Responses have been reported in both heavily and minimally pretreated ovarian cancer patients (20 – 37%) [57]. However, myelotoxicity was found to be a major concern even with granulocyte colony-stimulating factor support. In order to minimise toxicity, paclitaxel can be given weekly instead of every 3 weeks [58,59]; this results in a higher dose intensity of the drug [58]. Two non-randomised trials [61,62] have suggested that the activity of

paclitaxel in epithelial ovarian cancer is dose-dependent, and a randomised trial [58] has shown reduced toxicity with weekly scheduling without detriment to efficacy. It has been reported that single weekly paclitaxel has moderate activity in heavily pretreated ovarian cancer patients, and 80 mg/m² of paclitaxel was recommended as the Phase II dose for out-patients [63]. With 80 mg/m² of paclitaxel, the dose intensity may not be greater than once every three weeks. However, continuous low-dose paclitaxel has been reported to result in antiangiogenic effects and tumour dormancy [64,65]. Thus, the effects of single weekly paclitaxel in heavily pretreated patients with recurrent or persistent ovarian cancer were investigated. Thirty-seven patients were included in this intent-to-treat study. The overall clinical response rate was 45.9% (5 complete responses, 12 partial responses). The clinical response rate in patients with measurable tumour was 25.0% (2 complete responses, 1 partial response), whereas that in patients without measurable tumour and with assessable cancer antigen 125 (CA125) levels was 56.0% (3 complete responses, 11 partial responses). The criteria for response was based on declining CA125 levels as described by Rustin *et al.* [66]. Clinical response rates in patients with chemotherapy-free interval of > 6 months were around twice those found in patients with chemotherapy-free interval of < 6 months. The clinical response rate by number of prior regimens revealed that as number of prior regimens increases, the response rate decreases. Weekly paclitaxel has significant antitumour activity in heavily pretreated patients with recurrent or persistent ovarian carcinoma, and may be used as second- or third-line chemotherapy in such a setting [34]. Likewise, weekly administration of docetaxel has demonstrated comparable efficacy together with reduced myelosuppression in patients with solid tumours, including breast tumour, but not ovarian cancer [67].

4. Neoadjuvant chemotherapy

The clinical basis of aggressive cytoreductive surgery in the initial management of ovarian cancer is the significantly improved survival accrued to those patients in whom optimal cytoreductive surgery was accomplished [68,69]. The theoretical basis for primary cytoreductive surgery is supported by tumour cell growth kinetics observations that: an increase in cell-doubling time occurs as cancer becomes larger; resection of large tumour masses increases the number of residual cells that are in an active growth phase and are more sensitive to chemotherapy; and surgical cytoreduction results in an exponential reduction of tumour volume, thus leaving fewer cells to be eradicated [70]. These observations would suggest that neoadjuvant chemotherapy should, if anything, impair survival of women with advanced ovarian cancer. Some retrospective studies failed to demonstrate this as is shown in Table 1.

Although the prognosis for patients with advanced ovarian cancer has been improving over the last decades, long-term survival figures are still disappointingly low. More adequate therapeutic approaches need to be developed, especially for

patients whose tumours cannot be optimally debulked upfront. One such approach is the concept of chemical cytoreduction before debulking surgery in selected patients. Based on the available data, neoadjuvant chemotherapy in advanced ovarian cancer seems to allow for higher optimal debulking rates without compromising survival, and might be a valid alternative to upfront debulking surgery in patients with a high total metastatic load, stage IV disease, the presence of uncountable peritoneal metastases, or a poor performance status [71,72]. Some studies suggest that additional benefits may be reduced perioperative morbidity and increased quality of life. Hence, even if neoadjuvant chemotherapy followed by debulking surgery does not result in a better but similar overall survival compared with conventional treatment, it still may be a worthwhile approach based on considerations of morbidity, economic cost and quality of life. Some patients with primarily chemoresistant disease might also be spared the burden of an unnecessary laparotomy. All these issues have undoubtedly to be tested in a prospective randomised fashion. Until the results of such evaluations are available, neoadjuvant chemotherapy should not be considered as part of standard therapy in patients with advanced ovarian cancer, for whom the standard of care is still upfront maximal debulking surgery by an appropriately trained and experienced gynaecological oncologist.

5. Metronomic chemotherapy

Chemotherapeutic drugs, which have long been the mainstay of cancer treatment, cause DNA damage and disrupt DNA replication in proliferating cells. Drug regimens have been designated to kill as many tumour cells as possible by treating with MTDs of these cytotoxic agents. Side effects such as neurotoxicity and damage to proliferating cells in healthy tissues pose serious constraints on the use of chemotherapy. In an effort to balance toxicity with efficacy, a conventional dosing schedule calls for episodic application of a cytotoxicity drugs at or near the MTD, followed by periods of rest to allow normal tissues to recover. Many such chemotherapy regimens are initially efficacious, resulting in tumour regression or stabilisation and prolonged survival. In general, however, responses are short-lived, with relapses often marked by aggressive cancer that is resistant to the cytotoxic drug. Furthermore, the standard MTD regimen as a rule seriously impairs quality of life.

Although the collateral damage inflicted on the dividing bone marrow progenitors, gut mucosal or hair follicle cells by DNA damaging of microtubule inhibiting agents is certainly undesirable, the same cannot always be said of the damage inflicted on endothelial cells present in a tumour's growing neovasculature. A proportion of these cells are dividing at any given time, making them, at least in theory, sensitive to drugs that preferentially damage or destroy cycling cells [73]. Polverini's group first reported antiangiogenic effects mediated by conventional cytotoxic anticancer drugs as long ago as 15 years, and

since then most common anticancer chemotherapeutic agents, belonging to all major classes, have been shown to be capable of inhibiting angiogenesis [74]. This prompted Sledge and colleagues [64] recently to suggest the notion of 'redefining' chemotherapeutic drugs as antiangiogenics. It is intriguing and perhaps reassuring to note that there are many clinical precedents for the observations of Browder *et al.*, as summarised recently by Kamen *et al.* [75], and by Gately and Kerbel [76]. For example, significant proportions of breast and ovarian cancer patients ($\leq 62.5\%$) who had stopped responding to MTDs of a taxane given once every 3 weeks, were subsequently found to respond to the same drug once it was switched to a weekly schedule at about a third of the MTD [58,77-79]. Such weekly schedules using lower drug doses were instituted to minimise the toxicities associated with once-every-3-weeks MTD taxane protocols. It is not yet known whether the responses observed in these 'resistant' patients have an antiangiogenic basis, or whether such increased response rates will translate into a significant prolongation of survival, as they do in mice [80,81].

Introduction of paclitaxel into the armamentarium of drugs to treat platinum-resistant ovarian cancer has been one of the more significant advances in the treatment of ovarian cancer in the last decade. Paclitaxel has a unique mechanism of action, is cell-cycle-specific, and acts by promoting the stability of the microtubule assembly during mitosis. *In vitro* data suggest that the duration of exposure plays a crucial role in the cytotoxicity efficacy of paclitaxel [82,83]. Resistance to paclitaxel-mediated P-glycoprotein [84] has been shown to be significantly reduced by increasing the duration of exposure to paclitaxel from 3 to 96 h in P-glycoprotein-expressing paclitaxel-resistant breast cancer cell lines [85]. Weekly administration of paclitaxel has the potential to have an effect similar to that of continuous infusion while taking advantage of the minimal haematological toxicity associated with shorter infusions [34]. Neutropenia was the most frequent haematological adverse event observed in patients receiving once-weekly intravenous paclitaxel monotherapy. Severe neutropenia was dose-related, occurring only in 3 – 15% of patients receiving 80 mg/m² monotherapy [86,87]. An absolute neutropenia count of 1000 has been shown to be sufficient for dosing weekly paclitaxel on any given scheduled day of treatment. In this study, severe neutropenia and leukopenia of grade 4 were observed in 2 (5.4%) and 1 (2.7%) of 37 patients, respectively. Other haematological adverse events such as grade 4 anaemia and/or grade 4 thrombocytopenia were not observed. Neuropathy is experienced by most patients receiving once-weekly intravenous paclitaxel monotherapy and is usually mild or moderate [86,87]. Treatment with single weekly 80 mg/m² paclitaxel brought about an overall response rate of 45.9%, which is similar to that of a recent report [88]. It is noteworthy that 5 complete responses among 37 patients with one or more therapeutic regimens were achieved.

The choice of second-line drug in this present setting is dependent on toxicity and quality of life considerations, in

Table 2. HER-2/neu and EGFR overexpression rate according to histological type.

Histology	HER-2/neu overexpression	EGFR overexpression
Serous	8/60 (13%)	24/60 (40%)
Endometrioid	0/15 (0%)	4/15 (27%)
Mucinous	2/11 (18%)	2/11 (18%)
Clear	6/26 (23%)	11/26 (42%)
Total	16/112 (15%)	41/112 (36%)

EGFR: Epidermal growth factor receptor; HER-2: Human epidermal growth factor receptor 2.

addition to efficacy. Weekly administration of paclitaxel by 1-h infusion has been reported to have less toxicity than other schedules and primary effect in patients with pretreated gynaecologic cancers [58,60,89,90]. In addition, a randomised Cancer and Leukemia Group B trial comparing the weekly schedules to paclitaxel given once every 3 weeks for advanced breast cancer is nearing completion. 'Metronomic' dosing or antiangiogenic scheduling of cancer chemotherapeutics has been increasingly recognised to be a potential application of paclitaxel in cancer therapy [91-93].

6. Molecular-targeted chemotherapy

Traditional cytotoxic agents cannot distinguish malignant from nonmalignant cells. As a result, use of these agents at clinically effective doses is often accompanied by severe toxicity. This lack of specificity has stimulated the development of a new breed of agents that primarily target growth and signalling processes in malignant cells and, thus, tend to be less toxic to normal cells than conventional cytotoxic therapies [94]. These specially engineered compounds largely target cell-membrane receptors that control the intracellular signal transduction pathways regulating cell proliferation and apoptosis, angiogenesis, cellular adhesion and cell motility.

6.1 Epidermal growth factor receptor inhibitors

The epidermal growth factor receptor (EGFR) is highly expressed in a variety of solid tumours, including ovarian cancer. Activation of the EGFR signalling pathways has been linked with increased cell proliferation, angiogenesis, metastasis and decreased apoptosis [95]. Preclinical studies have shown that blocking this pathway inhibits these processes both *in vitro* and *in vivo* and increases apoptosis of malignant cells, while having minimal effects on normal cell function. The authors' clinical studies revealed that overexpression of EGFR was observed in 36% of ovarian cancer and seemed to be greater in serous cystadenocarcinoma and clear cell carcinoma than in endometrioid adenocarcinoma and mucinous cystadenocarcinoma, although not significant (Table 2).

The anti-EGFR therapies currently undergoing clinical development are the monoclonal antibodies trastuzumab (Herceptin®,

Genentech, Inc.) and cetuximab and small-molecule EGFR tyrosine kinase inhibitors gefitinib and erotinib (OSI-774/Tarceva™, OSI Pharmaceuticals, Inc.). Proliferation of ovarian epithelial cancer cells expressing HER-2/neu is blocked by trastuzumab *in vitro* [96], and the results of clinical testing at Ohio State University in ovarian cancer patients were shown to be inactive because of a small percentage of HER-2/neu-overexpressing tumours. In an immunohistochemical study, rate of HER-2/neu overexpression in ovarian cancer was 15%, and it is noteworthy that overexpression of HER-2/neu in endometrioid carcinoma was not observed, whereas clear cell carcinoma showed a higher staining rate (Table 2). A Phase I study of its safety in patients with a variety of tumours, including ovarian cancer, established that the drug was well-tolerated at doses of ≤ 600 mg/day and that treatment inhibited the EGFR signalling pathway [97].

Objective antitumour responses and evidence of disease stabilisation were documented in 34 patients with advanced platinum- and/or paclitaxel-resistant ovarian cancer who had been treated with erotinib [98].

6.2 Signal transduction inhibitors

Aberrant signal transduction has been implicated in malignant transformation, growth and progression. This has led to the proposal to use inhibitors of signal transduction pathways to treat cancer. Chronic myelogenous leukaemia (CML), for example, is characterised by a translocation between chromosomes 9 and 22. The fusion of the *Abl* gene on chromosome 9 with the *Bcr* gene on chromosome 22 forms a *Bcr-Abl* fusion gene that expresses tyrosine kinase, which is thought to be leukaemogenic. Imatinib mesylate (STI-571/Gleevec®, Novartis Pharmaceuticals Corporation) is a potent inhibitor of *Bcr-Abl* tyrosine kinase and selectively kills *Bcr-Abl*-expressing tumour cells. Recent studies have shown that several tumours express c-KIT: a growth factor receptor with tyrosine kinase activity; moreover, clinical results have shown the efficacy of the tyrosine kinase inhibitor, imatinib mesylate, in c-KIT-positive tumours. Intense c-KIT immunostaining was observed in 51.7% of cases. c-KIT expression was statistically correlated with progression of disease after first-line chemotherapy. c-KIT is also expressed in ovarian carcinoma and it is statistically correlated with chemotherapy resistance. Clinical trials confirming the utility of the tyrosine kinase inhibitor, imatinib mesylate, in advanced ovarian cancer patients with c-KIT overexpression who have shown no clinical response to conventional chemotherapy are warranted [99]. Clinical trials of imatinib mesylate in ovarian cancer are being conducted by the Gynecologic Oncology Group (GOG), National Cancer Institute and the Southwest Oncology Group. The PI3K/AKT pathway stimulates cell proliferation, inhibits apoptosis and increases drug resistance. The upregulation of the P110- α catalytic subunit of PI3K is often found in human ovarian cancer [100]. Kudoh *et al.* (pers. commun.) observed marked sensitising effect of PI3K inhibitor LY-294002 (Calbiochem) on antitumour effect of paclitaxel in a

paclitaxel-resistant human ovarian cancer cell line. The synergistic augmentation of the cytotoxicity by PI3K inhibitor LY-294002 occurs specifically with antimicrotubule agents, at least partially through an increase in caspase 3-dependent apoptosis, so that inhibitors of the PI3K/AKT pathway in combination with antimicrotubule agents may induce cell death effectively and be a potent modality to treat patients with malignant tumours [101]. PI3K inhibitor is a promising therapy strategy in drug-resistant ovarian cancer [102].

6.3 Antiangiogenesis therapy

Angiogenesis, the formation of new blood vessels, is essential to the growth and proliferation of solid tumours. Presumably, anything that interferes with angiogenesis will cause the tumour to 'starve' and eventually kill it, a concept originally proposed by Folkman [103]. Tumour angiogenesis may be regulated by angiogenic factors such as VEGF [104] and IL-8 [105]. Of the known proangiogenic factors, VEGF is one of the most potent and specific, and it has been identified as a crucial regulator of both normal and pathological angiogenesis. Overexpression of VEGF has been demonstrated in most human cancers, including ovarian tumours. Bevacizumab is a recombinant anti-VEGF monoclonal antibody that recognises all biologically active isoforms of VEGF and blocks their binding to VEGF receptors, thus inhibiting angiogenesis [104]. A Phase II clinical trial, designed and implemented by the GOG protocol 170D, is currently underway to assess the safety and efficacy of bevacizumab in patients with recurrent or persistent ovarian cancer. Also being investigated as a potential antiangiogenesis agent in ovarian cancer is thalidomide, which is showing some benefit in women refractory to conventional chemotherapy [106], and RPI-4610 (Angiozyme, Sirna Therapeutics, Inc.), a proprietary ribozyme that can downregulate VEGF receptor function by specifically cleaving the mRNA for a primary VEGF receptor: FLT-1. Clinical trials are currently in progress to establish the therapeutic efficacy and safety of RPI-4610 in patients with advanced malignancies. Extensive preclinical studies have demonstrated no significant toxicities [107]. Another antiangiogenic molecule under development is the PKC- β inhibitor LY-317615. This small, orally available molecule has demonstrated the ability to inhibit growth-factor-driven proliferation of tumour neovascularisation and is currently undergoing Phase I testing in several tumour types [108]. Recently, it has been reported that bisphosphonates (pamidronate) induce significant and lasting modifications of angiogenic cytokine patterns [109]. Experimental trials should be addressed to assess the real clinical impact in anticancer therapy of antiangiogenic properties of bisphosphonates.

The inducible enzyme cyclooxygenase-2 (COX-2) is an important mediator of angiogenesis and tumour growth. Selective COX-2 inhibitor drugs, commonly prescribed for pain management, are now being evaluated for their antitumour and antiangiogenic activities. These drugs include celecoxib (Celebrex[®], Pfizer, Inc.), rofecoxib (Vioxx[®], Merck

& Co, Inc.) and valdecoxib (Bextra[®], Pfizer, Inc.). Oral celecoxib (30 mg/kg/day) inhibited angiogenesis by 79% in a rat model of basic fibroblast growth factor (bFGF)-induced corneal angiogenesis, and reduced corneal levels of prostaglandin E2 and thromboxane 2 by 79 and 68%, respectively [110]. Celecoxib can also inhibit angiogenesis via COX-2-independent mechanisms. Impaired VEGF gene expression and decreased angiogenesis result from celecoxib-induced interference with DNA binding of the Sp1 transcription factor [111]. Celecoxib has also been reported to increase serum levels of the endogenous angiogenesis inhibitor endostatin, while decreasing the release of VEGF by platelets [112], thus altering the balance of angiogenesis regulation in favour of inhibition. A Phase II study of lung cancer patients receiving celecoxib 400 mg b.i.d. p.o. concurrently with paclitaxel/carboplatin plus radiation therapy found that serum/plasma levels of VEGF declined at 2, 5 and 7 months following treatment [113]. Rofecoxib also has been shown to inhibit angiogenesis in a number of *in vivo* systems. Administration of rofecoxib blocks the production of bFGF and reduces wound healing angiogenesis in experimental gastric ulcers [114]. In a model of retinopathy, rofecoxib inhibited neovascularisation in COX-2-expressing retinal vessels [115]. Based on supportive preclinical data, a large-scale clinical trial is underway in Europe studying rofecoxib as an adjuvant antiangiogenic treatment in 3500 patients with previously resected colorectal cancer. Although no clinical trials in ovarian cancer have been carried out, trials in such an adjuvant setting are awaited.

7. Conclusion

The management of ovarian cancer begins with appropriate surgical staging. Following surgical staging and removal of the reproductive organs, adjuvant chemotherapy has been performed. The standard regimen over the past several years has been a combination of carboplatin (area under the curve: 5 – 7.5) plus paclitaxel (175 mg/m², infused over 3 h). Studies carried out by GOG, as well as several European trials, have demonstrated optimum response rates with this combination, and it has come to be accepted as the 'gold standard' for treating ovarian cancer. Although this regimen has resulted in prolongation of survival times, only modest improvement of overall survival has been observed with this treatment strategy.

Recurrent ovarian cancer patients with platinum-refractory disease can still respond to platinum retreatment following treatment with continuous low-dose paclitaxel. In patients with platinum-resistant disease the use of intervening therapy to extend the platinum-free interval may be a useful strategy, providing a similar immediate response rate and an improved response to platinum later.

At present, solid evidence demonstrating the superiority of neoadjuvant chemotherapy followed by postdebulking chemotherapy over conventional postdebulking chemotherapy alone is lacking, but further study is needed. Elderly and medically