表1　NAC療法のmeta analysisによる解析

	Bristow (2006)	Kang (2009)
選択規準	1) Stage Ⅲ/Ⅳ>90% 2) NAC regimen included CDDP or CBDCA 3) NAC was administered before cytoreductive surgery	
Medline検索対象期間	1989.1.1～2005.9.30	1989.1.1～2008.6.30
試験数	21	21
背景因子などの平均（症例数を加味）		
生存期間中央値	24.5 M	27.5 M
タキサン系使用割合	47.7%	48.2%
Optimal手術達成率	65.0%	70.0%
Ⅳ期症例の割合	27.4%	28.9%
年齢	61.1 years	60.4 years
予後因子		
報告年	p=0.004 [1.1 M/year]	p=0.002
タキサン系使用割合	p<0.0005 [1.6 M/10%]	p=0.007
Optimal手術達成率	p=0.012 [1.9 M/10%]	p=0.012
Ⅳ期症例の割合	p=0.002 [−2.3 M/10%]	p=0.101 (NS)
NACのコース数	p=0.046 [−4.1 M/cycle]	p=0.701 (NS)
年齢	p=0.448 (NS)	NA
統計的手法	Simple linear regression model	Random-effects model
特記事項	NAC療法の成績は，初回手術でsuboptimal (>1 cm) となり，術後6コースのCP療法を受けたGOG試験参加症例と同等	NAC後のIDSでsuboptimalとなるriskはPDSと比して有意に減少 (Risk 0.5, 95% CI：0.29～0.86, p=0.012) [10試験での解析]
共通して含まれる試験 (14試験)	Jacob (1991), Lim (1993), Schwartz (1999), Kayikçioğlu (2001), Ansquer (2001), Kuhn (2001), Vrščaj (2002), Ushijima (2002), Chan (2003), Morice & Brehier-Ollive (2003), Mazzeo (2003), Avril (2005), Hegazy (2005), Le (2005)	
片方のみ含まれる試験 (7試験)	Donadio (1989), Tummarello (1990), Vergote (1998), Shibata (2003), Morice & Dubernard (2003), Fanfani (2003), Loizzi (2005)	Everett (2006), Lee (2006), Deo (2006), Inciura (2006), Steed (2006), Hou (2007), Colombo (2009)

NS：not significant, NA：not assessed, CP：cisplatin＋cyclophosphamide

齢（p=0.04）であったが，手術時出血量，ICU滞在期間，入院期間などにおいて，治療侵襲の軽減が認められ，MST，無増悪生存期間中央値（progression free survival；PFS）とも標準治療群と遜色のない予後が得られた。Lee ら[5]は，CT，MRIによりNAC群を決定，NACに同意しなかった人に標準治療を行った。NAC療法群では，出血量の有意な軽減が認められ（p=0.04），有意に（p=0.04）高率にoptimal surgeryが達成できた。予後は，MST，DFSとも標準治療群と同等であった。

いずれの試験も，期待するほど臓器切除や合併症の頻度には差は認めなかったが，NAC療法では出血量の軽減や，ICU滞在，入院期間の短縮が認められ，標準治療と同等あるいは同等以上の予後が期待される結果といえる。

表2　NAC 療法と手術先行治療の non-randomized 比較試験

Studies	Kuhn（2001）			Hegazy（2005）			Lee（2006）		
比較因子	標準治療（n＝32）	NAC 療法（n＝31）	p value	標準治療（n＝32）	NAC 療法（n＝27）	p value	標準治療（n＝22）	NAC 療法（n＝18）	p value
患者背景									
年齢	66（中央値）	61（中央値）	NS	53.6	58.7	p＝0.04	46.8	45.0	NS
Performance Status 2							7 例	5 例	NS
Ⅳ期症例				18 例	16 例	NS	2 例	2 例	NS
腫瘍縮小手術									
IDS 施行割合		97%（30/31）			67%（18/27）			100%（18/18）	
Optimal 定義	＜2 cm	＜2 cm		＜1 cm	＜1 cm		＜2 cm	＜2 cm	
Optimal surgery 達成割合	63%（20/32）	84%（26/31）	p＝0.04	62%（20/32）	48%（13/27）	NS	46%（10/22）	78%（14/18）	p＝0.04
出血量				735 m*l*	420 m*l*	p＝0.02	1061 m*l*	620 m*l*	p＝0.04
輸血量中央値	2 U	2 U	NS						
平均手術時間	270 min	260 min	NS	190 min	150 min	NS			
ICU 滞在期間				4.4 days	1.7 days	p＝0.03			
入院期間				15.9 days	10.5 days	p＜0.05	10.4 days	9.7 days	NS
臓器切除									
腸切除	11 例	9 例	NS	合わせて 11 例	合わせて 4 例	NS	3 例	1 例	NA
その他の臓器切除							2 例	0 例	NA
合併症									
術後腸閉塞	3 例	0 例	NS						
創部感染				2 例	2 例	NS			
創部縫合不全	1 例	3 例	NS						
発熱＞3 days	7 例	2 例	NS	7 例	1 例	NS			
膀胱炎	2 例	1 例	NS						
無気肺	1 例	1 例	NS	1 例	1 例	NS			
胸水				2 例	0 例	NS			
血栓症，塞栓症	1 例	1 例	NS	3 例	1 例	NS			
予後									
生存期間中央値	23 M	42 M	p＝0.007	28 M	25 M	NS	55 M	53 M	NS
無増悪生存期間中央値				19 M	21 M	NS	17 M	15 M	NS
患者選択規準，背景など									
NAC 群の選択	対象は，多量の腹水（＞500 m*l*）を有する卵巣癌ⅢC 期に限定。臨床試験に同意が得られなかった症例に標準治療。			試験開腹，腹腔鏡による切除可能性の評価により NAC 療法群を決定。合併症による手術不適例は含まず。			CT，MRI により切除可能性を評価し，NAC 群を決定。NAC に同意しなかった人が，標準治療。		
患者背景のばらつき	背景因子に有意差なし。			NAC 群は有意に高齢（p＝0.04）。			背景因子に有意差なし。		
NAC 群の IDS 適応	肺塞栓発症の 1 症例を除いて IDS 施行。			SD，PD の 9 例には IDS 施行せず。			SD も含めて，全例に IDS 施行。		

NA：not available，NS：not significant，SD：stable disease，PD：progressive disease

3. その他のNAC療法の第Ⅱ相試験

NAC療法の有用性と安全性を検証する第Ⅱ相試験も行われている。イタリアのRecchiaら[6]は，卵巣癌Ⅳ期症例34例に対して，CBDCAを含むregimenで，6コースのうち4コースをNACで行うNAC療法の第Ⅱ相試験を行った。SD，PDを除いた28例（82%）にIDSを行い，全例が残存腫瘍なしとすることができた。有害事象は軽度であった。MSTは28Mで，Ⅳ期症例としては良好な予後が得られたとしている。Japan Clinical Oncology Group（JCOG）の婦人科腫瘍グループでは，Ⅲ/Ⅳ期卵巣癌，卵管癌，腹膜癌に対してNAC療法のfeasibility試験（JCOG0206）を行った[7][8]。化学療法はPC（PTX+CBDCA）で，術前4コース，術後4コースとした。この試験では，CT，MRIなどの画像診断，穿刺液の細胞診，腫瘍マーカーによる診断により56人が登録され，腹腔鏡診断の結果，53人がⅢ/Ⅳ期の対象疾患であることが確認され，NACが行われた。SD以上の効果の47例（89%）にIDSを行い，38例（72%）が残存腫瘍<1 cm，うち29例（55%）が残存腫瘍0とすることができた。37例（70%）が治療完了し，22例（42%）が完全腫瘍消失（治療完了し，CA125<20かつ画像診断にて病変なし）に至った。安全性においても重篤な有害事象は認められなかった。NAC療法の有効性と安全性が確認され，画像診断，穿刺液の細胞診，および腫瘍マーカーにより，NAC療法の対象となる症例を的確に診断できることが確認された。Pölcherら[9]は，多量の腹水（>500 m*l*）を有する，生検にて確認されたⅢC/Ⅳ期卵巣癌症例を対象にNAC療法の第Ⅱ相試験（PRIMOVAR）を行った。この試験では化学療法DC（DTX+CBDCA）6コースのうち，NAC2コース群とNAC3コース群の比較も行った。治療開始された適格例88例のうち，患者拒否と合併症症例を除く83例（94%）にIDS施行，62例（70%）が残存腫瘍<1 cm，うち31例（35%）が残存腫瘍0に至った。血液毒性は高度であったが，全体に治療は安全で，64例（73%）が治療完了できた。NAC2コース群と，NAC3コース群では，MST，PFSに有意差は認めなかった。残存腫瘍（なし），腹水減少（<500 m*l*），CA125減量（>50%）が有意な予後因子であった。

4. NAC療法と手術先行治療の第Ⅲ相無作為比較試験

進行卵巣癌に対するNAC療法の役割を確定するためには，NAC療法と現在の標準治療である手術先行治療の第Ⅲ相比較試験が必要である。これまでに，ヨーロッパの臨床試験グループや，JCOGおよびインドの施設において，第Ⅲ相試験が開始されていることが知られている（表3）。European Organization for Research and Treatment of Cancer（EORTC）のVergoteらは，retrospective studyでのNAC療法の好成績を踏まえて，他に先駆けて，1998年より第Ⅲ相無作為比較試験としてEORTC55971を行った[10]。卵管癌，腹膜癌は，組織学的所見，化学療法感受性，予後が卵巣癌とほぼ同一であり，卵巣，卵管の摘出なしでは鑑別診断困難であることから，卵巣癌，卵管癌，腹膜癌のⅢC/Ⅳ期を対象にしている。

Royal College of Obstetricians and Gynaecologists（RCOG）のKehoeらは，Medical Research Council Clinical Trials Unit（CTU-MRC）との共同で，Chemotherapy or Upfront Surgery（CHORUS）第Ⅱ/Ⅲ相試験を行っている[11]。第Ⅲ相部分は2004年から開始された。最終的な試験デザインは，EORTC登録症例と合わせた約1,250症例で非劣性での解析予定である。この試験では，画像診断と腫瘍マーカー（CA125/CEA rate>25）のみで登録可としているが，この試験を紹介する論文や発表はほとんどなく，その根拠や詳細は現時点では不明である。

JCOGでは，Feasibility試験であるJCOG0206試験の良好な結果を受け，「Ⅲ期/Ⅳ期卵巣癌，卵管癌，腹膜癌に対する手術先行治療vs化学療法先行治療のランダム化比較試験」（JCOG0602）を，2006年より行っている（図

表3　NAC対標準治療の第Ⅲ相試験

試験グループ	EORTC	RCOG/CTU-MRC	JCOG	All India Institute of Medical Sciences
試験名	EORTC55971	CHORUS	JCOG0602	ID I473
中心国	Belgium	United Kingdom	Japan	India
研究代表者	Vergote, I. B.	Kehoe, S.	Yoshikawa, H.	Kumar, L.
対象疾患	卵巣癌，卵管癌，腹膜癌	卵巣癌，卵管癌，腹膜癌	卵巣癌，卵管癌，腹膜癌	卵巣癌
進行期	ⅢC/Ⅳ期	Ⅲ/Ⅳ期	Ⅲ/Ⅳ期	ⅢC/胸水Ⅳ期
試験のタイプ	第Ⅲ相	第Ⅱ/Ⅲ相	第Ⅲ相	第Ⅲ相
悪性の確認方法	（登録前）腹腔鏡生検あるいは針生検	画像診断および腫瘍マーカーにより診断，（登録後）針生検，腹腔鏡生検，穿刺細胞診	（登録前）穿刺細胞診	（登録前）細胞診，組織診
化学療法種類	Platinum製剤（CDDP or CBDCA）＋Taxane製剤（PTX or DTX）	CBDCAを含む化学療法	PTX＋CBDCA（TC療法）	PTX＋CBDCA（TC療法）
NAC群の化学療法回数	NAC 3コース＋Ope後3コース	NAC 3コース＋Ope後3コース	NAC 4コース＋Ope後4コース	NAC 3コース＋Ope後3コース
症例数	704	150（第Ⅱ相）＋400（第Ⅲ相）	300	180
開始	1998.9.21	2004.3（第Ⅲ相）	2006.11.17	2001.11
予定登録期間	4年間	4年間（第Ⅲ相）	3年間	約5年間
登録状況	2006.12.6登録完了	登録中	登録中	登録中
試験デザイン	非劣性	EORTC試験の704例と合わせて，約1,250例で非劣性	非劣性	（おそらく）非劣性
主な臨床試験登録番号	NCT00003636	NCT00075712	UMIN000000523	NCT00715286
臨床試験登録日	1999.11.1	2004.1.9	2006.11.17	2008.7.14

EORTC：European Organization for Research and Treatment of Cancer，JCOG：Japan Clinical Oncology Group，RCOG：Royal College of Obstetricians and Gynaecologists，CTU-MRC：Medical Research Council Clinical Trials Unit，CHORUS：Chemotherapy or Upfront Surgery

1)[12]。JCOG0206の結果より，画像診断，細胞診，腫瘍マーカーによる診断にて登録し，診断的腹腔鏡は行わずPDSあるいはNACに割り振っている。

インドのKumarらは，2001年から卵巣癌のⅢ期および胸水Ⅳ期症例を対象に第Ⅲ相比較試験を開始した。早期に開始されていたが，現在も継続中で，他の試験に遅れて2008年に臨床試験登録が行われた。

これら四つの試験のうち，EORTC試験は2006年に登録を完了し，2008年10月に行われたIGCS（International Gynecologic Cancer Society）のmeetingにて，prematureな解析結果が発表された[13]。また，Kumarらは，症例登録途中の解析結果を2006年[14]，2007年[15]のAmerican Society of Clinical Oncology（ASCO）で発表している（表4）。どちらの試験においても，NAC療法群においては，手術先行群に比して合併症が軽減されているが，高率にoptimal surgeryが達成できて，同等のPFSや

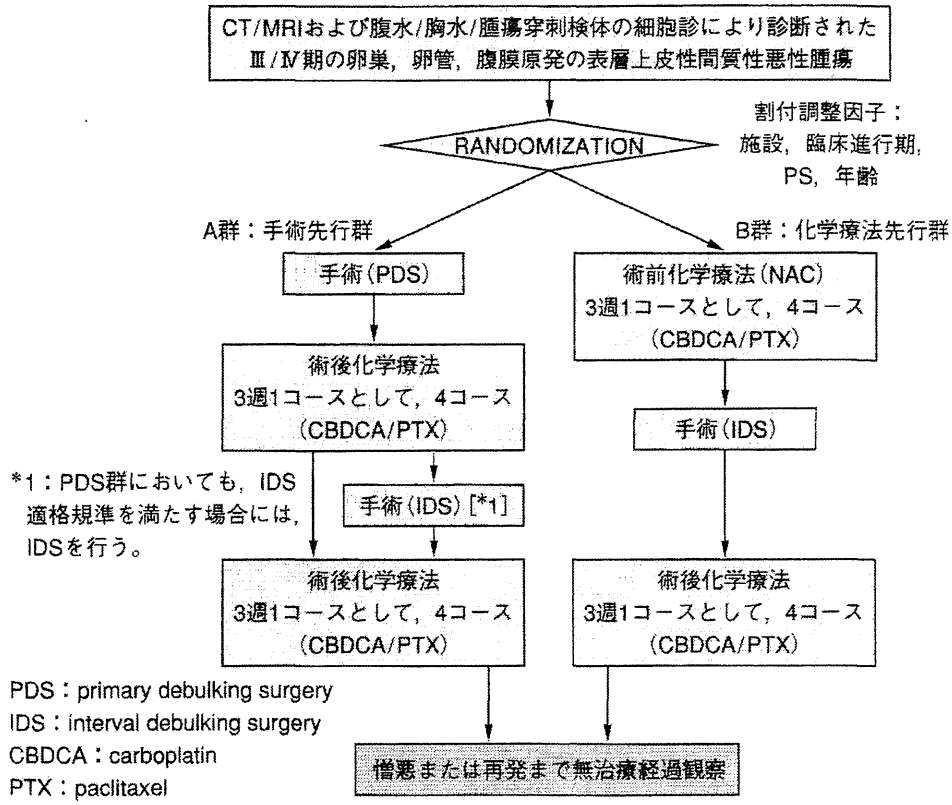

図1　JCOG0602 シェーマ

MST が得られている。また，詳細は不明であるが，Kumar らは質問票を用いた解析により，QOL が有意に改善したとしている。これらの結果は，いまだ正式なものではないが，他の試験も合わせた四つの試験の最終解析結果により，NAC 療法の効果が標準治療に劣らず（非劣性），手術侵襲や合併症などの軽減が示されれば，NAC 療法が進行卵巣癌の新しい標準治療になるものと考えられる。

III. NAC 療法における課題

NAC 療法の有用性に関しては，第Ⅲ相試験の結果が出揃うことが待たれるところであるが，標準治療として NAC 療法を施行する場合（あるいは，PS 不良例や切除不能例に対する代替的治療として施行する場合も），今後検討されなければならない課題が残されている。一つは，IDS の目標（optimal surgery の定義）である。従来 optimal surgery の定義として，PDS と同じ定義（<1 cm）が広く用いられてきた。われわれは，PDS 施行後に第二次手術を受けた症例の残存腫瘍と予後の関連から，化学療法施行後に行われた手術終了時に残存腫瘍を有する場合には微小残存（<2 cm）であっても長期予後は困難であることを示し，IDS においては残存腫瘍 0 を目標（optimal surgery）とすべきと報告している[16]が，前述のように，実際の NAC 療法施行例で，残存腫瘍 0 の予後が有意に良好とする報告もあり[9]（ただし，対照は残存腫瘍あり），今後の解析により明らかとなっていくと思われる。

その他にも，診断の確認方法，化学療法抵抗性の組織型（明細胞腺癌，粘液性腺癌）の取り扱い，臨床進行期の決定方法，最適な NAC のコース数，化学療法の種類，IDS の適応の判定，術後化学療法のコース数など，今後検討が必要と考えられる。

表4　第Ⅲ相試験の中間結果概要

Studies	India (n=74, 途中経過, ASCO2006)			India (n=93, 途中経過, ASCO2007)			EORTC (n=716, 登録完了, IGCS2008)		
比較因子	標準治療	NAC 療法	p value	標準治療	NAC 療法	p value	標準治療	NAC 療法	p value
患者背景									
年齢中央値				50 years			62 years	62 years	NA
Performance Status 2							11%	12%	NA
最大転移腫瘍径中央値							80 mm	80 mm	NA
ⅢC 期症例							76%	76%	NA
腫瘍縮小手術									
Optimal surgery (<1 cm)	13%	83%	<0.001	NA	NA	<0.001	48%	83%	NA
出血量	485 m*l*	340 m*l*	<0.008	520 m*l*	373 m*l*	<0.003			
平均手術時間	77 min	69 min	0.22	110 min	95 min	0.12			
入院期間	12.4 days	9 days	0.04	12 days	9.4 days	0.1			
合併症									
治療関連死	7.7%	3.3%	0.38				2.7%	0.6%	NA
敗血症							8%	2%	NA
術後感染	17.5%	3%	<0.07	14.8%	2.5%	<0.04			
出血 Grade 3/4 (輸血)							7%	4%	NA
消化器障害 Grade 3/4	3.8%	4.5%	NS	3%	4%	NS			
骨髄抑制	9%	7%	NS	9%	7%	NS			
予後									
生存期間中央値	42 M	41 M	NS	42 M	29 M	0.07	29 M	30 M	NA
無増悪生存期間中央値	29 M	35 M	NS	20 M	25 M	0.11	11 M	11 M	NA
QOL									
QOL score (FACT-O 質問票)	NA	NA	<0.001	93	114	<0.01			

ASCO：American Society of Clinical Oncology, EORTC：European Organisation for Research and Treatment of Cancer, IGCS：International Gynecologic Cancer Society, QOL：quality of life, FACT-O：Functional Assessment of Cancer Therapy-Ovarian, NA：not available, NS：not significant

おわりに

進行卵巣癌に対するNAC療法は，多くのretrospective studyによる良好な治療成績から，現在の標準治療である手術先行治療に代わりうる治療であると期待され，non-randomizedのprospective比較試験，第Ⅱ相，第Ⅲ相の臨床試験などが行われ，その有効性が検証されてきた。第Ⅲ相試験に関しては，いまだ最終結果が得られたものはないが，最初の第Ⅲ相比較試験であるEORTC試験の最終結果が近々明らかになろうとしている。第Ⅲ相試験の結果が出揃うことにより，NAC療法の有用性に関しては明らかとなると考えられるが，NAC療法を実施するにあたって，IDSの目標（optimal surgeryの定義）など，今後さらに検討を行っていく必要があると考えられる。

文　献

1) Bristow RE, Chi DS : Platinum-based neoadjuvant chemotherapy and interval surgical cytoreduction for advanced ovarian cancer : a meta-analysis. Gynecol Oncol, **103** : 1070-1076, 2006.
2) Kang S, Nam BH : Does neoadjuvant chemotherapy increase optimal cytoreduction rate in advanced ovarian cancer? Meta-analysis of 21 studies. Ann Surg Oncol, **16** : 2315-2320, 2009.
3) Kuhn W, Rutke S, Späthe K, et al : Neoadjuvant chemotherapy followed by tumor debulking prolongs survival for patients with poor prognosis in International Federation of Gynecology and Obstetrics Stage ⅢC ovarian carcinoma. Cancer, **92** : 2585-2591, 2001.
4) Hegazy MA, Hegazi RA, Elshafei MA, et al : Neoadjuvant chemotherapy versus primary surgery in advanced ovarian carcinoma. World J Surg Oncol, **3** : 57, 2005.
5) Lee SJ, Kim BG, Lee JW, et al : Preliminary results of neoadjuvant chemotherapy with paclitaxel and cisplatin in patients with advanced epithelial ovarian cancer who are inadequate for optimum primary surgery. J Obstet Gynaecol Res, **32** : 99-106, 2006.
6) Recchia F, De Filippis S, Rosselli M, et al : Primary chemotherapy in stage Ⅳ ovarian cancer. A prospective phase Ⅱ study. Eur J Gynaecol Oncol, **22** : 287-291, 2001.
7) Onda T, Kamura T, Ishizuka N, et al : Feasibility study of neoadjuvant chemotherapy followed by interval cytoreductive surgery for stage Ⅲ/Ⅳ ovarian, tubal and peritoneal cancers : Japan Clinical Oncology Group Study JCOG0206. Jpn J Clin Oncol, **34** : 43-45, 2004.
8) Onda T, Kobayashi H, Nakanishi T, et al : Feasibility study of neoadjuvant chemotherapy followed by interval debulking surgery for stage Ⅲ/Ⅳ ovarian, tubal, and peritoneal cancers : Japan Clinical Oncology Group Study JCOG0206. Gynecol Oncol, **113** : 57-62, 2009.
9) Pölcher M, Mahner S, Ortmann O, et al : Neoadjuvant chemotherapy with carboplatin and docetaxel in advanced ovarian cancer--a prospective multicenter phase Ⅱ trial (PRIMOVAR). Oncol Rep, **22** : 605-613, 2009.
10) Vergote IB, De Wever I, Decloedt J, et al : Neoadjuvant chemotherapy versus primary debulking surgery in advanced ovarian cancer. Semin Oncol, **27** : 31-36, 2000.
11) Kehoe S : Treatments for gynaecological cancers. Best Pract Res Clin Obstet Gynaecol, **20** : 985-1000, 2006.
12) Onda T, Matsumoto K, Shibata T, et al : Phase Ⅲ trial of upfront debulking surgery versus neoadjuvant chemotherapy for stage Ⅲ/Ⅳ ovarian, tubal and peritoneal cancers : Japan Clinical Oncology Group Study JCOG0602. Jpn J Clin Oncol, **38** : 74-77, 2008.
13) Vergote I, Tropé CG, Amant F, et al : EORTC-GCG/NCIC-CTG randomised trial comparing primary debulking surgery with neoadjuvant chemotherapy in stage ⅢC-Ⅳ ovarian, fallopian tube and peritoneal cancer (OVCA) (Abstract #1767). in Proceedings of the 12th biennial meeting of The International Gynecologic Cancer Society, Bangkok, Thailand. 2008.
14) Kumar L, Hariprasad R, Kumar S, et al : Neoadjuvant chemotherapy in advanced epithelial ovarian oancer (EOC) : A phase Ⅲ randomized study. J Clin Oncol (Meeting Abstracts), **24** : 15000, 2006.
15) Kumar L, Hariprasad R, Kumar S, et al : Neoadjuvant chemotherapy (NACT) followed by interval debulking surgery versus upfront surgery followed by chemotherapy (CT) in advanced epithelial ovarian carcinoma (EOC) : A prospective randomized study--Interim results. J Clin Oncol (Meeting Abstracts), **25** : 5531, 2007.
16) Onda T, Yoshikawa H, Yasugi T, et al : The optimal debulking after neoadjuvant chemotherapy in ovarian cancer : proposal based on interval look during upfront surgery setting treatment. Jpn J Clin Oncol, **40** : 36-41, 2010.

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Editorial

Overview on the 1st International Workshop on Gynecologic Oncology

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The 1st International Workshop on Gynecologic Oncology organized by Asian Society of Gynecologic Oncology (ASGO) was held at Clinical Research Institute of Seoul National University Hospital in Seoul, Korea, July 31st and August 1st, 2010 (Fig. 1). On behalf of the members of Asian Society of Gynecologic Oncology, I would appreciate President of ASGO, Soon- Beom Kang and Korean colleagues for organizing the 1st International Workshop on Gynecologic Oncology. The aim of this workshop was to give an opportunity to young colleagues to know the present status of gynecologic oncology in Asia. Here I would like to review the workshop. The workshop comprised of five sessions, prevention of cervical cancer, new trends of cervical cancer management, surgical technique, endometrial cancer, special lecture concerning clinical trial, and ovarian cancer. In the first session, cervical cancer prevention was highlighted. First professor Mohamad F. Aziz from Indonesia presented an overview about cervical cancer screening in Asia. He stressed that in few countries in South Eastern Regions cervical cancer screening program that have fully support by their government, and in less developed countries most of cervical intraepithelial neoplasia (CIN) lesions are treated with cryotherapy following visual inspection with acetic acid (VIA). Next professor Uma Devi impressed us her great effort to screen for cervical cancer in India. She also stressed VIA would be a suitable screening method in low resource setting. However, since it is difficult ensure screening at regular intervals, she recommend human papillomavirus (HPV) test at ten years intervals as another alternative screening method. Lastly professor Hextan YS Ngan updated our knowledge about HPV vaccine. Both bivalent and quadrivalent vaccines showed more than 90% of efficacy in preventing CIN2/3. And she concluded that both vaccines are effective and safe, and should be considered population vaccination of girls before sexual debut. An importance of cervical cancer screening is stressed as the protection after vaccination is not complete.

In the second session, treatment of cervical cancer was discussed. professor Jong Hyeok Kim overviewed the history of radical hysterectomy. Professor Seung Cheol Kim talked about fertility-sparing radical tracherectomy and less radical surgery that takes in neoadjuvant chemotherapy. Dr. Tomoyasu Kato presented how to preserve autonomic nerves in Okabayashi method. Professor Hee-Sug Ryu reviewed historical studies concurrent chemoradiotherapy (CCRT) for locally advanced cervical cancer. He introduced the ongoing prospective study conducted by KGOG in attempt to ascertain the effectiveness of paclitaxel and carboplatin as a CCRT regimen for patients with high risk factors for recurrent disease after radical hysterectomy. We look forward to seeing the final results of the study.

As a luncheon seminar, professor Young-Tak Kim mentioned cost-effectiveness of HPV vaccination and proposed that ASGO should contribute in building a consensus to urge inclusion of HPV vaccination in National Immunization Programs in Asia.

In the third session was a film session of various surgical techniques presented by the experts; nerve sparing radical hysterectomy by professor Shingo Fujii, optimal staging in early ovarian cancer by professor Dae Gy Hong, laparoscopic radical hysterectomy by professor Jong Hyeok Kim, one-port surgery by professor Tae Joong Kim, and robotic surgery by Young Tae Kim. Every technique should be understood by young doctors who will become leaders in the future.

The fourth session was focused on endometrial cancer. Professor Kung-Liahng Wang, introduced meta-analysis of four randomized studies comparing laparoscopy versus laparotomy in endometrial cancer, and concluded that until mature data from GOG and LACE trials become available, the role of laparoscopy as a standard treatment for endometrial cancer is still debatable. Regarding a role of lymphadenectomy in the management of endometrial cancer, professor Taek Sang Lee suggested that systematic lymphadenectomy is effective in detecting micro or occult metastasis, and thus improve surgical staging and make it possible to accurately pre-

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Fig. 1. Commemorative photograph of the 1st international workshop of ASGO.

dict the prognosis. Professor Kimio Ushijima presented the multi-institutional prospective phase II study regarding high dose medroxyprogesterone acetate (MPA) therapy for early endometrial cancer in the patients who desire for baby. The results shown were that CR rate for stage Ia endometrial cancer is 55% and that for atypical hyperplasia is 82%.

For special lecture, professor Sang-Goo Shin gave us a very interesting lecture that highlighted past historical experience of globalization and current status of clinical trials especially in northwest Asian countries, and stressed that Asian market is growing and promising for pharmaceutical companies.

The final session was assigned to ovarian cancer. Professor Yin Nin Chia talked about a history of first-line chemotherapy and the promising results of resent studies such as ip chemotherapy, dose-dense chemotherapy and Bevacizumab-added chemotherapy. Professor Sarikapan Wilailak reviewed neoadjuvant chemotherapy about rationale, meta-analysis, and prospective randomized studies. She concluded that neoadjuvant is best suited for patients with medical co-morbidities not able to undergo cytoreductive surgeries and for patients deemed to have unresectable disease. Professor Sang Yoon Park highlighted the procedure of surgical cytoreduction for advanced-stage ovarian cancer as well as recurrent ovarian cancer. He reminded us that gynecologic oncologist would live surgery. Professor Hidetaka Katabuchi was reviewed characteristics of ovarian cancer from the molecular aspect. His talk gave us a better understanding about translational research regarding ovarian cancer treatment.

In conclusion, this workshop was a great success in educating young colleagues by reviewing state of the art technology and indicating future direction for the treatment of gynecologic cancer. I would like to thank Korean colleagues again for their hard work to prepare this workshop and look forward to the 2nd biennial meeting of ASGO.

Malignant Transformation Arising From Mature Cystic Teratoma of the Ovary

A Retrospective Study of 20 Cases

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Objectives: Mature cystic teratoma (MCT) of the ovary rarely undergoes malignant transformation (MT). Malignant transformation carries a significantly worse prognosis than epithelial ovarian cancer, regardless of whether postoperative chemotherapy or radiotherapy is applied. The rarity of this tumor has posed a significant challenge to developing standardized postoperative management protocols. The aim of this study was to review our experience with MT and to describe our current treatment practices.

Methods: A retrospective chart review of these patients was performed that identified 20 women treated for MT of MCT at our centers between 1988 and 2008.

Results: The median age was 52.5 (range, 29–77) years. Fifteen patients had squamous cell carcinoma (SCC), and 5 patients had other histological subtypes. The International Federation of Gynecology and Obstetrics stage distribution was as follows: 11 were stage I, 4 were stage II, 4 were stage III, and 1 was stage IV. All patients underwent an initial laparotomy. Eleven patients received adjuvant treatment: 8 were treated with chemotherapy, 2 with concurrent chemoradiation therapy, and 1 with radiation therapy. Platinum-based chemotherapy was the first-line regimen. The overall 1-year survival rate was 70%. Significant correlations between overall survival and age, stage, and residual tumor were presented ($P = 0.044$, $P = 0.0107$, $P < 0.0001$, respectively). Eight patients with advanced stage died of their disease. Four patients, however, were treated with adjuvant chemotherapy or concurrent chemoradiation therapy and survived more than 1 year. One stage III patient had a disease-free interval of 2 years. Two cases of SCC treated with combination platinum/taxane chemotherapy temporarily responded. In the other 2 cases of SCC, concurrent chemoradiation therapy with nedaplatin also resulted in tumor regression.

Conclusions: The prognosis of MT is highly dependent on age, stage, and optimal cytoreduction. Adjuvant treatment has not been standardized, although our experience supports the use of combination platinum/taxane chemotherapy.

Key Words: Malignant transformation, Mature cystic teratoma, Adjuvant therapy

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Mature cystic teratoma (MCT), the most common ovarian germ cell tumor, accounts for 10% to 20% of all ovarian tumors.[1–4] Malignant transformation (MT) occurs in 1% to 2% of MCT.[1–4] Although MT may occur in any of the embryonic germ layers, most MTs are squamous cell carcinoma (SCC). Although most patients with MCT are young, the incidence of MT peaks in the age range of 45 to 60 years.[1–5] Stage is the most important prognostic factor, with most survivors having early-stage disease.[1–4] The prognosis of MT is significantly worse than that of epithelial ovarian cancer, regardless of the use of adjuvant chemotherapy or radiotherapy.[1–9] Squamous cell carcinoma from MCT

TABLE 1. Patient and treatment characteristics of the 20 cases

No.	Age, yr	Histology	Grade	Stage	Primary Surgery	Residual Tumor	First-Line Treatment		Second-Line Treatment		OS	F/U
1*	66	AC	—	Ia	TAH + BSO	−					7	Lost
2*	35	SCC	1	Ia	TAH + BSO + PLA	−	POMP × 3	NE			171	NED
3†	77	SCC	—	Ia	TAH + BSO + OMT + LN sampling	−					31	NED
4*	53	SCC	3	Ia	TAH + BSO	−					19	NED
5*	61	SCC	—	Ia	TAH + BSO + PLA + PALA	−					5	NED
6‡	55	MM	—	Ia	TAH + BSO	−					74	NED
7‡	47	AS	—	Ia	TAH + RSO	−					160	NED
8‡	36	SCC	—	Ia	LSO	−					72	NED
9‡	37	SCC	—	Ic	TAH + BSO + OMT + LN sampling	−	CPT11+ CDDP × 3	NE			180	NED
10*	49	SCC	2	Ic	TAH + BSO + PLA	−	BIP × 3	NE			104	NED
11*	40	SCC	—	Ic	TAH + BSO + PLA + PALA + OMT	−	BIP × 6	NE			55	NED
12*	62	SCC	2	IIb	TAH + BSO	+	RT + wCDDP	PD			12	DOD
13*	47	SCC	1	IIb	Tumor resection	+	TC × 3	SD	RT + CDGP × 4	PR	16	DOD
14*	68	AS	—	IIc	TAH + BSO	+	CAP × 2	PD			4	DOD
15*	29	SCC	1	IIc	Tumor resection	+	TP × 3	SD	RT	PD	14	DOD
16*	59	SCC	1	IIIa	TAH + BSO + appendectomy	−	BIP × 3	PD	T × 3	PD	14	DOD
17*	75	AC	—	IIIb	Probe laparotomy	+					5	DOD
18*	41	SCC	3	IIIc	TAH + BSO + PLA + PALA + OMT	−	RT + wCDGP	NE			24	NED
19*	56	SCC	1	IIIc	Probe laparotomy	+					1	DOD
20*	57	SCC	3	IV	BSO + OMT	+	RT	PD			3	DOD

*Cases treated in institution 1; †Case treated in institution 2; ‡Cases treated in institution 3.

AC, adenocarcinoma; AS, adenosquamous cell carcinoma; BIP, chemotherapy consisting of bleomycin, ifosfamide, and cisplatin; BSO, bilateral salpingo-oophorectomy; CAP, chemotherapy consisting of cyclophosphamide, Adriamycin, and cisplatin; CPT11, irinotecan; DOD, die of disease; F/U, follow-up; MM, malignant melanoma; NE, not evaluated; NED, no evidence of disease; OMT, omentectomy; OS, overall survival (months); PALA, paraaortic lymphadenectomy; PLA, pelvic lymphadenectomy; POMP, chemotherapy consisting of peplomycin, vincristine, mitomycin C, and cisplatin; RT, radiation therapy; TAH, total abdominal hysterectomy; TC, chemotherapy consisting of paclitaxel and carboplatin; TP, chemotherapy consisting of paclitaxel and cisplatin; wCDDP, weekly cisplatin; wCDGP, weekly nedaplatin.

also carries a worse prognosis than primary SCC or SCC associated with endometriosis.[10]

The rarity of MT is a challenge to standardizing its treatment. Multiple cytotoxic agents have been shown to have some efficacy against SCC. Of these, cisplatin has the highest activity.[1–7] In light of its use in cervical SCC as well as in ovarian cancer,[11–14] we used platinum/taxane combination chemotherapy in our advanced-stage MT, with or without radiotherapy. Here, we report our retrospective review of the cases of 20 patients with MT treated at our institutions during a 20-year period and discuss our current treatment protocols and survival statistics.

MATERIALS AND METHODS

A review of admission records from 1988 to 2008 resulted in the identification of 20 women treated for MT arising from MCT of the ovary in the hospital of Tohoku University Graduate School of Medicine, Miyagi Cancer Center, and the hospital of Kinki University School of Medicine. A retrospective chart review was conducted, with information obtained from patients' medical reports.

The pathological diagnoses were confirmed by 2 of the authors (K.I. and T.T.). The data of histological type and tumor grade were obtained from histological preparations or histological reports. The tumor grade (SCC) was classified in only about 10 cases according to the Broder classification[15,16] because neither preparations nor tissue block could be obtained in other cases.

Overall survival was calculated from the time of initial admission for treatment of the ovarian tumor. Survival times of patients still alive or lost to follow-up were censored in June 2008. Survival curves were estimated using the Kaplan-Meier method. Survival differences and associations of overall survival with treatment and other patient characteristics were analyzed with a log-rank test. Response was assessed according to the Response Evaluation Criteria in Solid Tumors.[17] *Complete response* (CR) was defined as the disappearance of all target lesions with confirmation at 4 weeks. *Partial response* (PR) was at least 30% reduction in the sum of the longest diameter of target lesions, taking as reference the baseline study; this also was confirmed at 4 weeks. *Progressive disease* (PD) was defined at least 20% increase in the sum of the longest diameter recorded since treatment started or new lesions appeared. Patients who did not meet any criteria were considered to have *stable disease* (SD).

RESULTS

Patient characteristics are summarized in Table 1. The median age was 52.5 (range, 29–77) years. Nine patients (45%) were younger than 50 years old, and 11 patients (55%) were older than 50 years old. The following 4 histological subtypes were observed: 15 SCC, 2 adenocarcinoma, 2 adenosquamous cell carcinoma, and 1 malignant melanoma. The International Federation of Gynecology and Obstetrics (FIGO) stage distribution was as follows: 8 in stage Ia, 3 in stage Ic, 2 in stage IIb, 2 in stage IIc, 1 in stage IIIa, 1 in stage IIIb, 2 in stage IIIc, and 1 in stage IV.

All patients underwent surgery, and 14 (70%) of 20 patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy with or without pelvic and/or paraaortic lymphadenectomy. Four (20%) of 20 patients either had a biopsy only or a partial resection because of involvement of the pelvic peritoneum and omentum. Lymphadenectomy was performed in 7 patients. Positive pelvic lymphadenopathy was found in only 1 patient (case 18).

Variables found to have statistically significant correlations with overall survival on univariate analysis are shown in Table 2. Univariate analysis was performed on the following parameters: age (<50 vs >50), histological type (SCC vs other histological subtypes), stage of disease (stage I/II vs stage III/IV), and cytoreductive surgery (optimal vs suboptimal). Age, stage, and cytoreductive surgery significantly affected overall survival.

The 1-year overall survival rate in the 20 patients collectively was 70%. The 1-year overall survival rates according to the FIGO stage were as follows: stage I, 100% (9/9, except for 2 patients lost to follow-up for more than 1 year); stage II, 75% (3/4); stage III, 50% (2/4); and stage IV, 0% (0/1). The cases in stage I survived without recurrence and resulted in better prognosis than the cases in more advanced stages. In the Kaplan-Meier survival analysis, stage was associated with overall survival rate ($P = 0.0107$; Table 2).

Twelve of the 13 patients who were optimally cytoreduced had no evidence of disease recurrence; 11 of them were in stage I, and 1 was in stage IIIc. The stage IIIa patient (case 16) locally recurred in 2 months despite being optimally cytoreduced and receiving adjuvant chemotherapy. Death occurred in 8 patients (40%) with advanced disease. Seven of the 8 patients had residual carcinoma after initial surgery. Despite receiving adjuvant chemotherapy, all

TABLE 2. Variables and overall survival

Factor	Total (n)	Dead (n)	Mean Survival, mo	*P*
Age, yr	20	8		0.044
<50	9	2	15.8	
>50	11	6	9.8	
Histological type	20			0.762
SCC	15	6	13.6	
Non-SCC	5	2	4.8	
Stage	20			0.0107
I–II	15	4	14.7	
III–IV	5	4	7.4	
Residual tumor	20			<0.0001
Optimal	13	1	14	
Suboptimal	7	7	7.9	

Non-SCC, including adenocarcinoma, adenosquamous cell carcinoma, and malignant melanoma; optimal, no gross residual tumor; suboptimal, defined residual tumor.

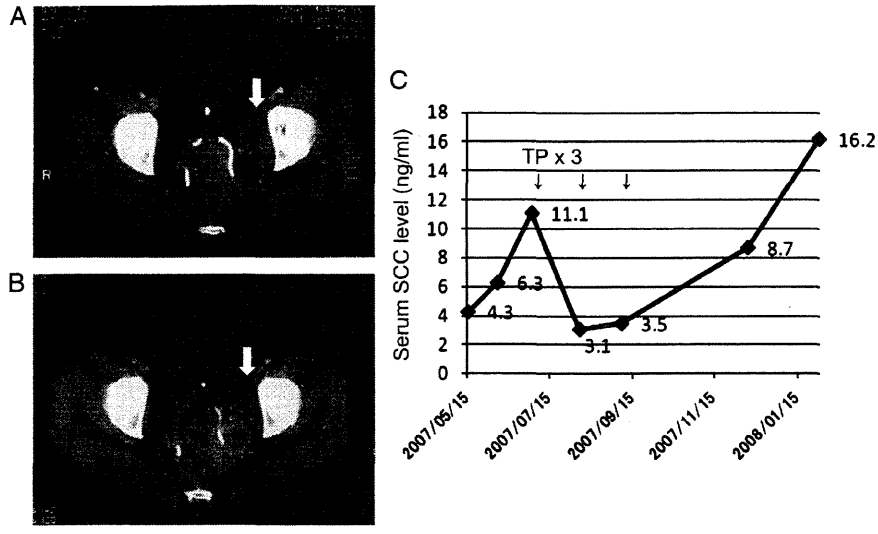

FIGURE 1. Response of chemotherapy for pelvic recurrent tumor after 3 courses of combination paclitaxel/cisplatin chemotherapy in patient 15. A, Pretreatment CT of pelvis shows the irregularly shaped tumor of the left pelvis. B, CT taken after the third course of cisplatin and paclitaxel at a similar level to the scan shown in (A) shows regression of the pelvic tumor. C, Responses of chemotherapy for serum SCC level in patient 15.

patients with residual tumors after their first debulking surgery died of their disease. Optimal versus suboptimal cytoreduction was associated with overall survival according to the log-rank test; mean survival of 14 (range, 5–180) months versus 7.8 (range, 1–16) months ($P < 0.0001$; Table 2). Optimal cytoreduction was associated with a statistically significant improvement in overall survival.

Regarding adjuvant therapy, 10 patients (50%) received platinum-based chemotherapy after their initial surgery, and 2 of them were concurrently treated with radiotherapy. No suboptimally cytoreduced patients achieved a CR despite adjuvant therapy; however, 4 of the 5 advanced-stage patients survived for more than 1 year after surgery. Two patients had SD while undergoing platinum/taxane chemotherapy (case 13 and case 15). When used concurrently with radiotherapy, nedaplatin induced regression of tumor growth in 2 patients (case 13 and case 18).

As for patient 15, she underwent radical hysterectomy, bilateral salpingo-oophorectomy, and tumor resection with Hartmann operation after initial laparotomy and pathological diagnosis. The residual tumor filled the pelvis, and vaginal bleeding developed 1 month after the second reductive surgery. She was treated with 3 cycles of 50 mg/m^2 cisplatin and 175 mg/m^2 paclitaxel at 21-day intervals. Upon completion of her chemotherapy, a computed tomographic (CT) scan revealed a partial reduction in the metastatic pelvic implant (Figs. 1A and B). The serum SCC level also fell from 11.1 to 3.1 ng/mL (Fig. 1C). We considered the response to be SD because the effect was temporary. She rapidly progressed and died despite the addition of radiotherapy.

Patient 13 was treated with concurrent chemoradiation therapy with nedaplatin after 3 cycles of adjuvant therapy with paclitaxel and carboplatin (TC). While on TC, her serum SCC level initially decreased, however, her disease progressed quickly. Concurrent chemoradiation therapy with nedaplatin after TC lowered serum SCC level and resulted in a 6-month progression-free interval (Fig. 2). We considered the response to be a PR.

Patient 18 received optimal cytoreduction and treated with concurrent chemoradiation with nedaplatin. She survived without evidence of disease for 2 years after treatment.

DISCUSSION

In this retrospective study, we reviewed the treatment and prognosis of 20 patients with MT arising in MCT treated during a 20-year period. In this report, we show that age, stage, and optimal cytoreduction are significantly correlated with prognosis of this disease. Although the number of cases in this review is small because of the rarity of the tumor, our results are consistent with prior studies.[1–7]

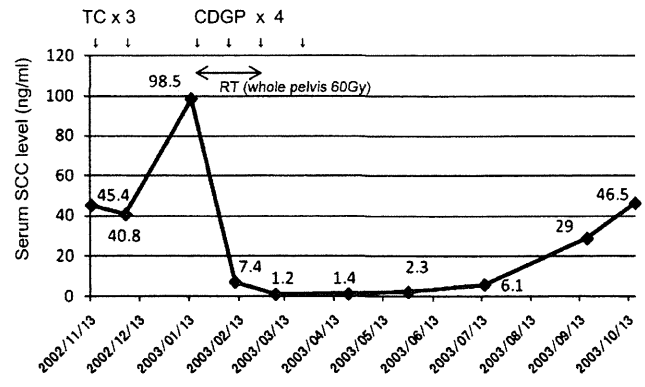

FIGURE 2. Responses to chemotherapy of serum SCC level in patient 13. TC, chemotherapy consisting of paclitaxel and carboplatin; CDGP, nedaplatin.

According to previous reports, Chen et al[6] reported that tumor optimal debulking was one of the factors that most significantly influenced survival. Tseng et al[7] reported that aggressive cytoreduction for advanced disease followed by adjuvant therapy might relate to good overall survival. We suppose that hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and retroperitoneal lymphadenectomy are recommended for complete surgical staging of this malignancy and optimal cytoreduction. In our institutions, hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and the pelvic and paraaortic lymphadenectomy or biopsy sampling are generally performed for this disease as well as epithelial ovarian cancer. Twelve of 13 patients with optimal cytoreduction had no evidence of recurrence of disease. But sometimes, the unexpected diagnosis is made during surgery or on final pathology in early-stage disease; indeed, our several cases in early stage have not received surgical staging surgery. On the other hand, patients of childbearing age with early-stage disease wish to be managed with conservative surgery and oophorocystectomy or unilateral oophorectomy. Chen et al[6] reported that the survival rate in stage Ia disease for oophorocystectomy/oophorectomy did not differ statistically from oophorectomy plus hysterectomy or retroperitoneal lymphadenectomy. Among our cases of stage Ia, 5 of 8 cases were treated without retroperitoneal lymphadenectomy, and 1 case (case 8) was managed with unilateral oophorectomy only. The patients survived without recurrence. These data might help consider the treatment options of patients with stage Ia disease who wish to keep the ability to get pregnant.

The optimal adjuvant therapy for this disease has not been established. Park et al[2] reported that patients with disease beyond the ovary who received adjuvant chemotherapy or concurrent chemoradiation therapy had longer survival times than those treated with surgery alone or with adjuvant radiation therapy alone. Chen et al[6] reported that postoperative adjuvant chemotherapy produced better results than adjuvant radiotherapy. Consistent with these studies, there was no response to radiotherapy in our patients.

The current use of platinum against MT is related to its known activity against epithelial ovarian cancer and SCC of the cervix.[11–14] In our institutions, we used chemotherapy and radiotherapy regimens for SCC arising in MCT, which were in use at the time for SCC of the cervix. In contrast, we treated adenocarcinoma arising in MCT in a manner similar to epithelial ovarian cancer. In this report, we discussed adjuvant therapy for cases with SCC because there was only 1 case with other histological types treated with adjuvant therapy. We expect that a common regimen regardless of histological type will be used for the standard adjuvant therapy if the combination chemotherapy with platinum/taxane is useful for SCC arising in MCT.

Platinum/taxane chemotherapy is generally accepted as the first-line chemotherapeutic agent for patients with epithelial ovarian cancer.[11,12] McGuire[13] and Zanetta et al[14] have also reported that paclitaxel has notable activity against SCC of the cervix. Recently, Yamagami et al[18] found, using the collagen gel droplet–embedded drug sensitivity test, that combination chemotherapy with paclitaxel and carboplatin was active in MT arising from MCT. We reviewed the English-language literatures and found 7 studies[1,2,19–23] that included 8 cases of SCC of the ovary treated with a combination of platinum and paclitaxel (Table 3). Most patients had an extended progression-free interval. Eltabbakh et al[19] and Ohtani et al[20] reported measurable responses to platinum/paclitaxel administration of abdominal metastatic tumors. These cases, however, were SCC of the ovary arising in association with ovarian endometriosis but not from MCT. Other studies failed to demonstrate measurable responses because there was no target lesion present after primary surgery.[1,2,21–23] This study is the first report indicating measurable responses to combination chemotherapy with platinum and paclitaxel in SCC arising from MCT.

Several recent studies have analyzed the efficacy and safety of concurrent chemoradiation therapy with weekly nedaplatin for the treatment of advanced SCC of the uterine cervix.[24–26] Kurita et al[27] reported that neoadjuvant chemotherapy with docetaxel and nedaplatin for oral SCC showed an overall response rate of 56.6% in histological assessment of surgical specimens. In our study, patient 18 received concurrent chemoradiation therapy using nedaplatin after an optimal cytoreductive surgery and had an overall survival of

TABLE 3. Case series of SCC of ovary received a combination chemotherapy of platinum and paclitaxel

Author	No. Patients	Median Age, yr	Stage	Residual Tumor	First-Line Adjuvant Treatment	Second-Line Adjuvant Treatment	F/U After Operation, mo
Eltabbakh et al[19]*	1	31	IV	+	TP (CR)		NED,24
Ohtani et al[20]*	1	53	II	−	POMB (PD)	wTC (CR)	NED, 15
Powell et al[21]	1	67	III	−	TP (NE)		NED, 57
Wen et al[23]	1	32	III	−	BEP	TC	DOD, 19
Dos Santos et al[1]	1	37	I	−	TC (NE)		NED, 3
Arioz et al[22]	1	31	II	−	TP (NE)		NED, 6
Park et al[2]	1	31	III		TP		NED, 23
	1	43	III		CCRT (TP)		NED, 13

*Case reports of SCC of ovary with ovarian endometriosis.

2 years. She was the only patient with advanced-stage disease who completely responded to treatment. A previous report showed that the 2-year disease-free survival was 30% for patients with stage III disease. Survival increased to 60% with optimal cytoreduction.[5] In contrast, another study reported that the 5-year survival rate for patients with stage III disease was 0%.[28]

Our result may support the future investigation of new regimens using nedaplatin for this malignancy.

In conclusion, MT arising from MCT is a rare malignancy with a poor prognosis. An optimal adjuvant treatment strategy has not been developed. Our review has shown that age, stage, and optimal cytoreduction are correlated with prognosis. The small study population makes it difficult to draw any definite conclusions regarding the impact of adjuvant chemotherapy; however, when considered in light of findings from studies, combination platinum/taxane chemotherapy may lead to improved survival in advanced-stage SCC arising from MCT. Future studies are needed to confirm our preliminary observations.

REFERENCES

1. Dos Santos L, Mok E, Iasonos A, et al. Squamous cell carcinoma arising in mature cystic teratoma of the ovary: a case series and review of the literature. *Gynecol Oncol.* 2007;105:321–324.
2. Park JY, Kim DR, Kim JH, et al. Malignant transformation of mature cystic teratoma of the ovary: experience at single institution. *Eur J Obstet Gynecol Reprod Biol.* 2008;141: 173–178.
3. Hackenthal A, Brueggman D, Bohlmann MK, et al. Squamous cell carcinoma in mature cystic teratoma of the ovary: systematic review and analysis of publish data. *Lancet Oncol.* 2008;9:1178–1180.
4. Hackenthal A, Brueggmann D, Bohlmann MK, et al. Erratum. *Lancet Oncol.* 2009;10:446.
5. Mori Y, Nishii H, Takebe K, et al. Preoperative diagnosis of malignant transformation arising from mature cystic teratoma of the ovary. *Gynecol Oncol.* 2003;90:338–341.
6. Chen RJ, Chen KY, Chang TC, et al. Prognosis and treatment of squamous cell carcinoma from a mature cystic teratoma of the ovary. *J Formos Med Assoc.* 2008;107:857–868.
7. Tseng CH, Chou HH, Huang KG, et al. Squamous cell carcinoma arising in mature cystic teratoma of the ovary. *Gynecol Onocol.* 1996;63:364–370.
8. Hirakawa T, Tsuneyoshi M, Enjoji M. Squamous cell carcinoma arising in mature cystic teratoma of the ovary. Clinicopathologic and topographic analysis. *Am J Surg Pathol.* 1989;13:397–405.
9. Chadha S, Schaberg A. Malignant transformation in benign cystic teratoma: dermoids of the ovary. *Eur J Obstet Gynecol Reprod Biol.* 1988;29:329–338.
10. Pins MR, Young RH, Daly WJ, et al. Primary squamous cell carcinoma of the ovary. Report of 37 cases. *Am J Surg Pathol.* 1996;20:823–833.
11. Omura G, Bleesing JA, Ehrlich CE, et al. A randomized trial of cyclophosphamide and doxorubicin with or without cisplatin in advanced ovarian carcinoma. A Gynecologic Oncology Group Study. *Cancer.* 1985;57:1725–1730.
12. 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.* 2000;92:699–708.
13. McGuire G. Paclitaxel has moderate activity in squamous cervix cancer. A Gynecologic Oncology Group study. *J Clin Oncol.* 1996;14:792–795.
14. Zanetta G, Fei F, Mangioni C. Chemotherapy with paclitaxel, ifosfamide, and cisplatin for the treatment of squamous cell cervical cancer: the experience of Monza. *Semin Oncol.* 2000;27:23–27.
15. Broders AC. Squamous-cell epithelioma of the skin. *Ann Surg.* 1921;2:141–160.
16. Kikkawa F, Ishikawa H, Tamahoshi K, et al. Squamous cell carcinoma arising from mature cystic teratoma of the ovary: a clinicopathologic analysis. *Obstet Gynecol.* 1997;89: 1017–1022.
17. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst.* 2000;92:205–216.
18. Yamagami W, Banno K, Kawaguchi M, et al. Use of the collagen gel droplet embedded drug sensitivity test to determine drug sensitivity against ovarian mature cystic teratoma with malignant transformation to adenocarcinoma: case report. *Chemotherapy.* 2007;53:137–141.
19. Eltabbakh GH, Hempling RE, Recio FO, et al. Remarkable response of primary squamous cell carcinoma of the ovary to paclitaxel and cisplatin. *Obstet Gynecol.* 1998;91:844–846.
20. Ohtani K, Sakamoto H, Masaoka N, et al. A case of rapidly growing ovarian squamous cell carcinoma successfully controlled by weekly paclitaxel-carboplatin administration. *Gynecol Oncol.* 2000;79:515–518.
21. Powell JL, Stinson JA, Connor GP, et al. Squamous cell carcinoma arising in a dermoid cyst of the ovary. *Gynecol Oncol.* 2003;89:526–528.
22. Arioz DT, Tokyol C, Sahin FK, et al. Squamous cell carcinoma arising in a mature cystic teratoma of the ovary in young patients with elevated carbohydrate antigen 19-9. *Eur J Gynaecol Oncol.* 2008;29:282–284.
23. Wen KC, Hu WM, Twu NF, et al. Poor prognosis of intraoperative rupture of mature cystic teratoma with malignant transformation. *Taiwan J Obstet Gynecol.* 2006;45: 253–256.
24. Yoshinaga K, Niikura H, Ogawa Y, et al. Phase I trial of concurrent chemoradiation with weekly nedaplatin in patients with squamous cell carcinoma of the uterine cervix. *Gynecol Oncol.* 2007;104:36–40.
25. Yokoyama Y, Takano T, Nakahara K, et al. A phase II multicenter trial of concurrent chemoradiation therapy with weekly nedaplatin in advanced uterine cervical carcinoma: Tohoku Gynecologic Cancer Unit Study. *Oncol Rep.* 2008;19:1551–1556.
26. Niibe Y, Tsunoda S, Jobo T, et al. Phase II study of radiation therapy combined with weekly nedaplatin in locally advanced uterine cervical carcinoma (LAUCC): Kitasato Gynecologic Radiation Oncology Group (KGROG 0501)—initial analysis. *Eur J Gynecol Oncol.* 2008;29:222–224.
27. Kurita H, Yamamoto E, Nozaki S, et al. Multicenter phase 2 study of induction chemotherapy with docetaxel and nedaplatin for oral squamous cell carcinoma. *Cancer Chemother Pharmacol.* 2010;65:503–508.
28. Kikkawa F, Nawa A, Tamakoshi K, et al. Diagnosis of squamous cell carcinoma aising from mature cystic teratoma. *Am Cancer Soc.* 1998;82:2249–2255.

Randomized Phase II Trial of Paclitaxel Plus Carboplatin Therapy Versus Irinotecan Plus Cisplatin Therapy as First-Line Chemotherapy for Clear Cell Adenocarcinoma of the Ovary

A JGOG Study

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Introduction: Paclitaxel plus carboplatin (TC) is generally considered to be the "gold standard" regimen for treatment of epithelial ovarian carcinomas. Little data are available, however, on the use of this regimen in patients with clear cell adenocarcinoma of the ovary (CCC). Combination chemotherapy with irinotecan hydrochloride plus cisplatin has been reported to be effective for primary and recurrent or resistant CCC. We compared these 2 combinations in patients with CCC.

Methods: Patients (n = 99) with CCC were randomly assigned to receive either 180 mg/m^2 paclitaxel on day 1 plus AUC 6 mg/mL × minute carboplatin on day 1 every 21 days (TC arm) or 60 mg/m^2 irinotecan hydrochloride on days 1, 8, 15 plus 60 mg/m^2 cisplatin on day 1 every 28 days (CPT-P arm).

Results: Percentages of patients receiving the scheduled 6 cycles of chemotherapy in the TC and CPT-P arms were 70.8% and 72.0%, respectively. Although toxicity was well tolerated in both arms, the toxicity profile of each arm differed. Progression-free survival (PFS) showed no significant difference between the 2 treatment groups. Because there were more patients with large residual disease in the CPT-P arm, we performed a subset analysis by removing those patients, and then compared the PFS with that of patients without residual disease or with residual disease less than 2 cm. The PFS tended to be longer in the CPT-P group, although the difference was not statistically significant.

Conclusions: A phase III randomized trial is required to elucidate the effectiveness of CPT-P combination chemotherapy for CCC.

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Clear cell adenocarcinoma of the ovary (CCC) has been recognized as a distinct histological entity under the World Health Organization classification of ovarian tumors since 1973. Clear cell adenocarcinoma of the ovary accounts for between 3.7% and 12.1% of all epithelial carcinomas, and its incidence is much higher in Japan than in the United States or Europe.[1–3] Many studies have shown that conventional platinum-based chemotherapy regimens such as cyclophosphamide plus cisplatin, cyclophosphamide plus cisplatin plus doxorubicin, and cyclophosphamide plus carboplatin yielded a poorer prognosis in patients with CCC than in patients with serous cystadenocarcinoma of the ovary.[1,4,5]

Paclitaxel plus carboplatin (TC) is generally considered to be the "gold standard" regimen for treatment of epithelial ovarian carcinomas according to the results of several randomized phase III trials.[6–8] This regimen has been used widely for all histological subtypes of epithelial ovarian carcinoma, including CCC. However, only 2% to 5% of the patients enrolled in these randomized trials had CCC.[6–8] Several retrospective and prospective studies have recently reported that response in measurable CCC cases treated with TC was relatively low, ranging from 22% to 56%.[9–11] The survival benefit of the TC regimen compared with conventional platinum-based regimens is also controversial; 1 study showed superior survival benefit,[12] whereas another implied no survival benefit in either early or advanced cases.[13]

Combination chemotherapy with irinotecan hydrochloride plus cisplatin (CPT-P) has been used clinically for patients with several types of human cancer. One large clinical trial, in particular, revealed that CPT-P showed significant activity for extensive small-cell lung cancer.[14] Moreover, it was reported that CPT-P therapy was effective for primary advanced and recurrent or resistant CCC.[2,3,15–17] One retrospective study also reported that progression-free survival (PFS) in CCC cases treated with CPT-P therapy was significantly better than in those treated with paclitaxel plus platinum.[17]

The Japanese Gynecologic Oncology Group (JGOG) conducted a randomized phase II study to compare CPT-P with TC in patients with CCC (JGOG3014).

MATERIALS AND METHODS

This phase II, centrally randomized, multicenter, open-label comparative trial included 37 independent investigative sites in Japan. A total of 99 patients were randomly assigned to either the TC or CPT-P treatment arm between January 2002 and July 2005. The study was performed in accordance with the principles of good clinical practice, applicable laws, and regulations, and the Declaration of Helsinki. Informed consent was obtained from all patients entered into the trial. Each institution obtained institutional review board approval of the protocol before study initiation.

Patient Eligibility

To be included in the study, patients had to have undergone surgery for ovarian carcinoma and the appropriate tissue be available for histological evaluation. Patients had to have histologically confirmed CCC and be at International Federation of Gynecology and Obstetrics (FIGO) stage Ic to IV, with or without residual disease after initial surgery. Stage Ic with capsule rupture during surgery was excluded. In cases where other histological cell types were concurrently present, clear cell histology had to be dominant. Histological diagnosis was confirmed by central pathological review after registration. Patients had to enter the study within 4 weeks of undergoing surgery, with no previous chemotherapy or radiation for ovarian cancer. Other eligibility criteria included written informed consent; an Eastern Cooperative Oncology Group performance status (PS) score of 0 or 1; aged 15 to 75 years; and adequate organ function. *Adequate organ function* (adequate function of the bone marrow, liver, and kidney) was defined as being indicated by a leukocyte count of at least 3000/μL, an absolute neutrophil count of at least 1500/μL, a hemoglobin level of at least 9.5 g/dL, a platelet count of at least 100,000/μL, a serum bilirubin level of less than 1.5 mg/dL, aspartate aminotransferase and alanine aminotransferase values of no more than twice the upper level of normal for the institution involved, and a creatinine clearance of at least 60 mL/min or serum creatinine level of less than 1.3 mg/dL when creatinine clearance was not applicable.

Exclusion criteria were as follows: serious concurrent disease of the liver, kidney, or heart; bone marrow suppression; systemic infection; diarrhea greater than National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade 1 (grade 2, 3, or 4); intestinal palsy; ileus; symptomatic brain metastasis; massive pleural or peritoneal effusion; a history of severe drug allergy; and pregnancy or breast-feeding. Patients with a history of other invasive malignancies, with the exception of nonmelanoma skin cancer and localized breast cancer, were excluded if there was any evidence of other malignancy being present within the previous 5 years.

Treatment Plan

Patients ware randomly assigned to either the paclitaxel plus carboplatin arm (TC) or the irinotecan hydrochloride

plus cisplatin arm (CPT-P) by the minimization method of balancing groups according to FIGO stage (I or II vs III or IV) and residual tumor size (<1 cm vs ≥1 cm). Randomization was performed at the JGOG data center according to the order in which information on enrollment was received by fax. Women in the TC arm received paclitaxel (180 mg/m^2) intravenously for 3 hours, followed by carboplatin (AUC 6 mg/mL × minute) intravenously for 1 to 2 hours on day 1 every 3 weeks for a total of 6 courses. The carboplatin dose was calculated using the Calvert formula; carboplatin dose (in milligrams) = AUC × (GFR + 25). The glomerular filtration rate was estimated using the Jelliffe formula. Patients assigned to the TC arm were premedicated with dexamethasone (20 mg intravenously 12–14 and 6–7 hours or 30 minutes before the start of paclitaxel infusion). Both diphenhydramine (50 mg orally) and ranitidine (50 mg intravenously) or famotidine (20 mg intravenously) were also administered 30 minutes before paclitaxel infusion. Patients in the CPT-P arm received irinotecan hydrochloride (60 mg/m^2) intravenously for 90 minutes on days 1, 8, and 15 and cisplatin (60 mg/m^2) intravenously for 1–2 hours on completion of irinotecan hydrochloride infusion on day 1 every 4 weeks for a total of 6 courses. Patients assigned to the CPT-P arm received prechemotherapy and postchemotherapy hydration to avoid cisplatin-induced nephrotoxicity. In all patients, antiemetic prophylaxis consisted of serotonin type 3 receptor antagonists and corticoids.

Dose Modifications and Modifications in Treatment Schedule

Adverse events were graded according to the NCI-CTCAE, version 2.0. Treatment modifications included skip, cycle delay, and dose reduction. Administration of irinotecan hydrochloride was skipped on day 8 or 15 if absolute neutrophil count was less than 1500/μL, if platelet count was less than 100,000/μL, or if there was grade 2 or higher diarrhea. Treatment in successive cycles was delayed if leukocyte count was less than 3000/μL, if absolute neutrophil count was less than 1500/μL, if platelet count was less than 100,000/μL, if creatinine clearance was less than 60 mL/min or serum creatinine level was 1.3 mg/dL and greater when creatinine clearance was not applicable, or if there was grade 2 or higher diarrhea. Otherwise, treatment in successive cycles could be recommenced with dose reductions in the TC arm (paclitaxel at 150 mg/m^2 and carboplatin AUC 5 mg/mL × minute) and CPT-P arm (irinotecan hydrochloride at 50 mg/m^2 and cisplatin at 50 mg/m^2) when the successive cycle was delayed for more than 2 weeks after the previous cycle if the patient had a leukocyte count of at least 2000/μL, an absolute neutrophil count of at least 1000/μL, a platelet count of at least 75,000/μL, a creatinine clearance of at least 50 mL/min or serum creatinine level less than 1.3 mg/dL when creatinine clearance was not applicable, and grade 1 or no diarrhea. Treatment was terminated if the next cycle was delayed for more than 2 weeks, if the leukocyte count was less than 2000/μL, if the absolute neutrophil count was less than 1000/μL, if the platelet count was less than 75,000/μL, if the creatinine clearance was less than 50 mL/min or serum creatinine level was 1.3 mg/dL and greater when creatinine clearance was not applicable, or if there was grade 2 or higher diarrhea.

Evaluations

All patients underwent weekly evaluations that included an assessment of symptoms, a physical examination, a complete blood cell count, and blood chemistry studies (including measurements of serum bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, and serum creatinine). Creatinine clearance was measured before each treatment cycle.

In patients with measurable disease, tumor response was evaluated according to World Health Organization criteria (1979) and assessed by computed tomography or magnetic resonance imaging, which was performed every 2 cycles. A *complete response* (CR) was defined as the disappearance of all clinical and radiological evidence of tumor for at least 4 weeks; a *partial response* (PR) was defined as a decrease of 50% or more in the sum of the products of the longest perpendicular diameters of all measurable lesions for at least 4 weeks; *progressive disease* (PD) was defined as an increase of more than 25% in the sum of the products of the perpendicular diameters of all measurable lesions or the appearance of new lesions. All other circumstances were considered to indicate *no change* (NC).

Statistical Analysis

The primary end point in this study was PFS, and the secondary end points were overall survival (OS), response rates, and adverse events. This was the first prospective study of CCC patients, and no retrospective analyses focusing on PFS or OS in a large number of such patients treated with TC or CPT-P therapy had been published before January 2002. Therefore, it was impossible to calculate the accrual sample size based on statistical method. Furthermore, response rate could not be established as the primary end point because usually most CCC patients have no measurable disease as assessed by computed tomography or magnetic resonance imaging after primary surgery. Therefore, we planned a phase II study to include 120 patients, with 60 patients in each group and PFS as the primary end point. The planned duration of accrual was 3.5 years, and the planned follow-up was 5 years. Only eligible cases with histologically confirmed CCC by central pathological review were included in the analysis of PFS, OS, and response rates. Only eligible women receiving at least 1 course of treatment were included in the assessment of adverse events.

All comparisons of patient characteristics, prognostic variables, response rates, and rates of adverse effects were performed with Fisher exact test, except for age, for which the Wilcoxon rank sum test was used. The PFS and OS were measured from the date of initial surgery. *Duration of PFS* was defined as minimum amount of time until clinical progression, death, or date of last contact. Duration of OS was measured up to the date of death or, for patients still alive, the date of last contact. Survival curves were calculated by the Kaplan-Meier method and compared with by the log-rank test. The multiple Cox regression model was used to explore the impact of specific prognostic factors on PFS.

RESULTS

Patient Characteristics

Initially, the sample size was planned to include 120 patients. However, this accrual target proved impossible to meet. Therefore, finally, we analyzed 99 patients enrolled during the 42-month planned accrual period (January 2002–July 2005). Fifty patients were assigned to the TC arm and 49 patients to the CPT-P arm. One patient in the CPT-P arm refused to allow submission of her case report form to the data center. Therefore, the full analysis sets (FASs) for the CPT-P and TC arms were 48 and 50 patients, respectively. After central pathology review, 5 cases were excluded because of wrong cell type, which included clear cell borderline tumor with microinvasion, serous borderline tumor with micropapillary pattern, transitional cell carcinoma, malignant mixed epithelial tumor (endometrioid adenocarcinoma, 75%; clear cell carcinoma, 25%), and endometrioid adenocarcinoma. One of them was in the CPT-P arm and 4 were in the TC arm. Therefore, an analysis for per protocol set (PPS) was performed for 47 patients in the CPT-P arm and 46 patients in the TC arm. The median follow-up time for this trial was 31.6 months.

Patient characteristics in FAS and PPS are shown in Table 1. Comparison of characteristics in FAS and PPS revealed a similar distribution in both treatment arms in terms of residual tumor less than or greater or equal to 1 cm, stages Ic-II or III-IV, age, and with or without complications. Nevertheless, PS was slightly poorer in the CPT-P arm, with 7 patients of 48 in FAS and 47 in PPS with PS 1, but only 1 patient with PS 1 in the TC arm (FAS, F = 0.044; PPS, F = 0.043). Although the number of patients in FAS and PPS was well balanced in terms of size of residual tumor greater or equal to 1 cm or less than 1 cm, there were more patients with residual tumor greater or equal to 2 cm in the CPT-P arm (11 patients compared with 4 patients in the TC

TABLE 1. Patient characteristics

	FAS (n = 98)			PPS (n = 93)		
Characteristic	**CPT-P (n = 48)**	**TC (n = 50)**	**Test**	**CPT-P (n = 47)**	**TC (n = 46)**	**Test**
Age, yr			W = 0.551			W = 0.900
Mean	54	58		54	54	
Range	31–70	33–75		31–70	33–75	
PS			F = 0.044			F = 0.043
0	40	48		39	45	
1	7	1		7	1	
Unknown	1	1		1	0	
Complications			F = 0.891			F = 1.000
Yes	8	7		8	7	
No	40	42		39	39	
Unknown	0	1		0	0	
FIGO stage			F = 0.833			F = 0.830
Ic–II	30	32		29	30	
III–IV	18	18		18	16	
Ic	25	22		24	22	
IIc	5	10		5	8	
IIIa	1	0		1	0	
IIIb	0	3		0	3	
IIIc	14	12		14	10	
IV	3	3		3	3	
Residual tumor			F = 0.321			F = 0.189
<1 cm	36	42		35	40	
≥1 cm	12	8		12	6	
Microscopic	30	34		29	32	
0 cm < < 1 cm	6	8		6	8	
1 cm ≤ < 2 cm	1	4		1	4	
≥ 2 cm	11	4		11	2	

F, Fisher exact test; W, Wilcoxon rank sum test.

TABLE 2. No. cycles by treatment

	CPT-P (n = 48)		TC (n = 50)	
Cycle	No. Patients	%	No. Patients	%
0	0	0	0	0
1	3	6.2	1	2.0
2	4	8.3	4	8.0
3	3	6.2	5	10.0
4	3	6.2	3	6.0
5	3	1.2	1	2.0
6	34	70.8	36	72.0

arm in FAS and 11 patients compared with 2 patients in the TC arm in PPS).

Treatment Administration

No significant differences were observed between the 2 groups in delivery of treatment (Table 2). The populations of patients in the TC and CPT-P arms in FAS who received the planned 6 cycles of chemotherapy were 70.8% (95% confidence interval [CI], 55.9–83.0) and 72.0% (95% CI, 57.5–83.8), respectively.

Adverse Events

Adverse events were graded according to the NCI-CTCAE, version 2.0. Major adverse events are shown in Table 3. None of the patients developed neutropenic fever. Incidence of grade 3 or worse leukopenia, neutropenia, anemia, and thrombocytopenia developed in 60.0%, 86.0%, 32.0%, and 24.0%, respectively, of the patients in the TC arm in FAS, and in 50.0%, 72.9%, 45.8%, and 4.2%, respectively, of the patients in the CPT-P arm in FAS. Grade 3 or worse thrombocytopenia occurred more frequently in the TC arm than in the CPT-P arm (odds ratio, 0.14; 95% CI, 0.03–0.65; $P = 0.0077$).

Grade 3 or worse nausea, vomiting, and diarrhea occurred in 16.0%, 8.0%, and 2.0%, respectively, of the patients in the TC arm in FAS, and in 31.3%, 16.7%, and 10.4%, respectively, of the patients in the CPT-P arm in FAS. Although

TABLE 3. Major adverse events

		No. Patients					% of Patients (95%CI)	Odds Ratio (95%CI)
		Grade						
Adverse Event	Treatment Arm (n)	1	2	3	4	3 or 4	3 or 4	3 or 4
Hematological								
Leukopenia	CPT-P (48)	5	19	22	2	24	50.0 (35.2–64.8)	0.67
	TC (50)	3	16	29	1	30	60.0 (45.2–73.6)	(0.30–1.48)
Neutropenia	CPT-P (48)	2	7	23	12	35	72.9 (58.2–84.7)	0.44
	TC (50)	2	3	12	31	43	86.0 (73.3–94.2)	(0.16–1.22)
Thrombocytopenia	CPT-P (48)	16	4	2	0	2	4.2 (0.5–14.3)	**0.14***
	TC (50)	26	5	9	3	12	24.0 (13.1–38.2)	**(0.03–0.65)***
Anemia	CPT-P (48)	4	15	19	3	22	45.8 (31.4–60.8)	1.80
	TC (50)	3	22	12	4	16	32.0 (19.5–46.7)	(0.79–4.09)
Nonhematological								
Nausea	CPT-P (48)	12	19	14	1	15	31.3 (18.7–46.3)	2.39
	TC (50)	20	17	8	0	8	16.0 (7.2–29.1)	(0.90–6.31)
Vomiting	CPT-P (48)	13	16	7	1	8	16.7 (7.5–30.2)	2.3
	TC (50)	14	10	4	0	4	8.0 (2.2–19.2)	(0.64–8.21)
Diarrhea	CPT-P (48)	12	10	5	0	5	10.4 (3.5–22.7)	5.7
	TC (50)	6	2	1	0	1	2.0 (0.1–10.6)	(0.64–50.69)
Alopecia	CPT-P (48)	25	17	—	—	—	—	
	TC (50)	11	38	—	—	—	—	
Peripheral motor neuropathy†	CPT-P (48)	6	5	0	0	5	10.4 (3.5–22.7)	0.53
	TC (50)	12	8	1	0	9	18.0 (8.6–31.4)	(0.16–1.71)
Peripheral sensory neuropathy†	CPT-P (48)	9	3	0	0	3	6.3 (1.3–17.2)	**0.19***
	TC (50)	29	12	1	0	13	26.0 (14.6–40.3)	**(0.05–0.72)***

Adverse events were graded according to NCI-CTCAE, version 2.0.
*Statistically significant difference between treatment arms.
†Incidence of neurotoxicities was calculated for grades 2/3/4.