表3　部位別のリンパ節転位頻度

	PLN (+) PAN (−)	PLN (+) PAN (+)	PLN (−) PAN (+)	PLN (−) PAN (−)	A	B	C	D
永野ら（1996年）（Ⅰ～Ⅲ）110例	5例	5	6	94	85.5%	9.1	50.0	6.0
吉川ら（1996年）（Ⅰ～Ⅳ）181例	11	22	3	145	80.1	18.2	33.3	2.0
嘉村（1996年）（Ⅰ～Ⅳ）174例	15	11	5	143	82.2	14.9	57.7	3.4
櫻木ら（1997年）（Ⅰ～Ⅲ）182例	22	14	2	144	79.1	19.8	61.1	1.4

A：全症例中でのPLN，PAN共に（−）の割合
B：全症例中でのPLN（+）の割合
C：PLNが.(+)でPAN（−）のもの
D：PLNが（−）でPANだけ（+）のもの

（矢嶋　聰ほか，2000[5]より引用）

うことになる．また，骨盤内リンパ節に転移がなくて，大動脈節だけに転移が認められたものの頻度は2～3%程度と考えられる．これらのことを考慮すると，子宮体癌では，傍大動脈リンパ節は2次リンパ節であるとの意見もある．Creasmanら[6]は多変量解析の結果，組織分化度，筋層浸潤の深さ，付属器以外の子宮外転移の3因子が独立して，リンパ節転移に強く影響を与えると述べており，上記のような因子をもとにしてリンパ節郭清を行うか否かを決定できれば，必要かつ充分な治療を行えると考える．

■■ 術後補助療法，寛解導入療法

現在，術後補助療法としては，主として放射線療法か，化学療法が選択されるが，明確な術後療法が確立していないのが現状である．

欧米では，手術進行期Ⅰ，Ⅱ期症例ではほとんど化学療法は行われておらず（1～2%），術後療法の主体は放射線療法（70～60%）である．Ⅲ期症例においても約60%に放射線療法が選択されている．しかし放射線療法はあくまで局所療法であり，子宮体癌でも遠隔転移再発がしばしば見られること，また腺癌に対する放射線感受性が扁平上皮癌ほど高くないことなどより，子宮頸癌のように術後療法として放射線療法が効果的であるのか疑問が生じる．一方，本邦では，Ⅰc，Ⅱb期ではともに約43%，Ⅲ期においても約59%の症例において化学療法が選択されている．第38回子宮癌研究会では[7]，子宮体癌の術後療法として，放射線療法と化学療法の比較が行われた．1994年以前の症例はrandomized-studyではないため，バイアスが存在しこれだけでは結論はできないが，予後因子別に比較したものでは両者の予後に明らかな差は見られていない．また，婦人科癌化学療法共同研究会の子宮体癌第4次研究では，術後の化学療法（CAP療法）と放射線療法を比較したrandomized-studyが実施されており，2000年12月に症例集積が終了した．今後その結果の一刻も早い公表が待たれるところである．

当教室においての治療方針を示す．まず，術後補助療法の適応基準は術後進行期Ⅰa期，Ⅰb期のなかでも組織学的分化度G3，脈管侵襲，特殊組織型（漿液性，明細胞腺癌など）を示すもの，およびⅠc期以上のものとしている．2002年4月までは，Ⅲ期までの補助療法として放射線療法を選択していた．しかし，PANまで施行した例にさらに放射線療法を追加した場合，高度な放射線障害が発生する頻度が増加したため，現在では追加療法を化学療法に変更した．化学療法の内容としては，Fist lineはCAP療法を選択している．子宮体癌に対し，単剤で効果が認められているも

のの奏効率を表4に示す[8]．Cisplatin，carboplatin，doxorubicinが比較的奏効率が高いが20～40%程度である．上記のような単剤での成績をもとに，種々の多剤併用療法が試みられており，CAP療法での有用性を示したものが多く，その奏効率は31～56%と比較的高い．Burkeら[9]は再発，または進行体癌に対してCAP療法を行ったところ奏効率45%で，初発例と再発例の間に差はなく，CAP療法は有効なレジメンであるとしている．しかしながら平均奏効期間は4.8カ月と短く，生存期間の延長はCR症例でもnon-responderと比較して平均10カ月である．

CAP療法にかわる薬剤として，paclitaxelが現在注目されている．GOG phase Ⅱ trialとしてBallら[10]は進行，再発子宮体癌30例に対するpaclitaxel 250mg/m²の24時間投与を行い，35.7%の奏効率を得ている．また，WooらはCDDP抵抗性の子宮体癌に対しpaclitaxel 170mg/m²/weekの3週間連続投与を施行し，43%の奏効率を報告している．Lissoniらは前治療としてCAP療法が行われ進行または再発症例19例を対象とした175mg/m²（3時間投与）の投与量の検討にて37%の奏効率を得ている．このなかでCAP療法でresistantであった症例においても22%（2

表4　子宮体癌に対する　単剤化学療法

抗癌剤		報告者	報告年	症例数	奏効数 (CR＋PR)	奏効率 (%)	奏効期間 中央値(月)
cyclophosphamide		Donovan	1974	25	7	28	−
		Pawinski (EORTC)	1999	14	0＋2	14	−
ifosfamide	(前治療あり)	Sutton (GOG)	1994	40	3＋3	15	3.9
	(前治療なし)	Sutton (GOG)	1996	37	2＋6	24	−
	(前治療なし)	Pawinski (EORTC)	1999	16	2＋2	25	−
cisplatin	(前治療あり)	Thigpen (GOG)	1984	25	0＋1	4	4.0
	(前治療あり)	Deppe	1980	13	2＋2	31	4.0
	(前治療なし)	Seski	1982	26	11	42	5.0
	(前治療なし)	Edmomson	1987	14	0＋3	21	2.0
	(前治療なし)	Thigpen	1989	49	2＋8	20	2.9
carboplatin		Long	1988	26	0＋7	27	4.3
		Green	1990	23	2＋5	30	4.8
		Burke	1993	27	3＋6	33	2.7
doxorubicin		Thigpen (GOG)	1979	43	11＋5	37	5.0
		Horton	1978	21	1＋3	19	−
epirubicin		Calero	1991	27	7	26	−
pirarubicin		Chauvergne J (EORTC)	1993	28	2＋0	7	−
dactinomycin		Moore (GOG)	1999	25	1＋2	12	−
fluorouracil		Devite	1976	43	10	23	−
etoposide (oral)	(前治療あり)	Rose (GOG)	1996	25	0	0	−
	(前治療なし)	Poplin (SWOG)	1999	44	1＋5	14	−
paclitaxel 175 (3 hr)	(前治療あり)	Lissoni	1996	19	2＋5	37	7＋
paclitaxel 170 (3 hr)	(前治療あり)	Woo	1996	7	0＋3	43	6.0
paclitaxel 250 (24hr)	(前治療なし)	Ball (GOG)	1996	28	4＋6	36	3.5
randomized trials							
doxorubicin		Thigpen (GOG)	1993	122	10+23	27	3.9
doxorubicin + cisplatin				101	22+23	45	6.2
doxorubicin		Thigpen (GOG)	1994	132	7+22	22	7.2
doxorubicin + cyclophosphamide				144	18+25	30	6.2

（進　伸幸ほか，2002[8]より引用）

/7）の奏効が得ていることは注目される．Priceら[11]はpaclitaxelとcarboplatinの併用療法を進行，再発子宮体癌に施行し，63%にPRが得られたと報告している．2000年には中村ら[12]が，Priceらと同治療法にて73%（16/24），2001年には衛藤らが67%（6/9）に奏効したと報告した．また予後不良とされる漿液性腺癌に対しても，Resnikら[13]は進行症例に対してpaclitaxelとcarboplatinの3 cycle投与によりPRが得られたと報告し，Zanottiら[14]は63%に奏効したと報告している．そこで，当科でも特殊組織型，再発例にpaclitaxelとcarboplatin（TJ療法）の併用療法を採用している．

■■ 若年体癌の取扱い

通常，若年内膜癌の若年とは40歳以下を指し，この年齢層は妊孕性の望まれる年齢層である．一般的に内膜癌はエストロゲンの関係するタイプⅠと関係しないタイプⅡに分けられる．若年女性はこのタイプⅠが多く，エストロゲンやプロゲステロン受容体陽性で，高分化型で，びまん性に発生し筋層浸潤が少なく，予後が良い．したがって，抗エストロゲン作用をもつMPA療法（酢酸メドロキシプロゲステロン）が有効である場合がある．当科では，妊孕性温存希望の異型内膜増殖症と臨床的子宮体癌Ⅰa期かつ組織分化度G1症例にのみ，充分なインフォームドコンセントを行ったうえで施行している．MPA（600mg/day）を内服し3ヵ月ごとに子宮内膜全面掻爬（D&C）を施行している．異型内膜増殖症においては治療後1回目のD&CにてPDの場合はMPA療法を中止し，2回目のD&CにてNC，PDの場合はMPA療法を続行する．CRの場合はMPA療法を終了している．癌においては，治療後1回目のD&CにてNC，PDの場合はMPA療法を中止し，2回目のD&CにてCR以外はMPA療法を中止する．CRの場合はMPA療法を終了している．治療終了後は子宮鏡検査を施行し，病変があれば，D&Cを施行している．原則的に1ヵ月ごとの細胞診，超音波，3ヵ月ごとの入院D&C，6ヵ月ごとのMRIでフォローし，2年間連続して異型細胞がでなかった時点で寛解としている．当科ではこれまで高分化型子宮体癌16例に体してMPA療法を行い11例，69%の奏効率を得ており，うち2例は妊娠分娩に至っている[15]．

■■ フォローアップ

フォローアップ間隔はローリスクとハイリスクにわけて行っている．ハイリスク群は進行期Ⅰc期以上，組織分化度grade 3，特殊組織型，不完全治療例としている．ローリスク群は2年目までは3ヵ月ごと，3年目は6ヵ月ごと，4年目以降は1年ごととしている．ハイリスク群は間隔を短くし，1年目は1～2ヵ月ごと，2，3年目までは3ヵ月ごと，4年目6ヵ月ごと，5年目以降1年ごととしている．体癌の再発部位としては，骨盤内では腟断端や子宮傍結合織近傍，腟壁再発が比較的多いことから，内診，直腸診，細胞診は毎回行っている．その他，毎回行う検査としては，超音波検査，体癌に特異的な血清腫瘍マーカーは見いだされていないものの，再発の早期発見にマーカーの測定は欠かせないことからCA125，CA19-9など，術前陽性マーカーを検査している．再発初発部位として肺，傍大動脈節以上の上位リンパ節，骨，肝，脳などの遠隔転移が50%を越えることより，6ヵ月毎に胸部から骨盤にかけてのCT検査を施行している．その他，再発の疑われる症例には骨，腫瘍シンチを行い，適宜，血清，生化学検査，骨盤MRI検査を施行している．

■■ おわりに

わが教室における子宮体癌の治療，フォローアップについて述べた．子宮体癌は近年増加傾向にあるが，その治療法においては一定の見解が得られておらず，進行癌，再発癌に対する奏効期間，生存期間とも満足する治療法が得られていないのが現状である．しかしながら，基本は早期発見，

早期治療であり，今後そのための診断技術の開発，進歩が望まれる．また，進行癌，再発癌に対しては，薬剤感受性，薬剤耐性マーカーなども考慮した新たな治療法の開発が待たれるところである．

文　献

1）今野　良ほか：子宮体癌；大動脈リンパ節郭清の意義．他施設アンケート調査の解析 63：1197−1202, 1996.
2）桜木範明ほか：子宮体癌治療上の問題点（予後もふくめて）．産婦実際 46：347−354, 1997.
3）澤　加奈子ほか：子宮体癌における頸部浸潤度とリンパ節転移の関係について．産婦実際 47：913−916, 1998.
4）Leimen A, et al：Endometrial adenocarcinoma with clinical evidence of cervical involvement；accur-acy of diagnostic procedures,clinical course, and prognostic factors. Acta Obstet Gynecol Scand 74：61−66, 1995.
5）矢嶋　聰ほか：子宮体癌の治療に広汎子宮全摘術や傍大動脈リンパ節郭清は必要か．産と婦 67：912−917, 2000.
6）Creasman WT, Morrow CP, Heller PB, et al：Surgic-Al pathologoc spread patterns of endometrical cancer；a Gynecologic Oncology Group study. Can-Cer 60：2035−2041, 1987.
7）山崎正明ほか：子宮体癌の補助化学療法の評価．産と婦 66：1180−1186, 1999.
8）進　伸幸ほか：子宮体癌の化学療法．産と婦 69：595−602, 2002.
9）Burke TW, et al：Prospective treatment of advanced or recurrent endometrial carcinoma with cisplatin, doxorubicin and cyclophospamide. Gynecol Oncol 40：264, 1991.
10）Ball HG, et al：A phase Ⅰ trial of paclitaxel in patients with advanced or reccurent adenocarcinoma of the endometrium；A Gynecologic Oncology Group Study. Gynecol Oncol 62：278, 1996.
11）Price, et al：A trial of outpatientpaclitaxel and carboplatin for advanced recurrent, and histologic high-risk endmetrial carcinoma：preliminary report. Semin Oncol 24：S15, 1997.
12）中村俊昭ほか：子宮体癌に対するpaclitaxelcarboplatin併用療法の効果．癌と化学療法 27：257, 2000.
13）Resnik E, et al：Neoadjjuvant chemotherapy in uterine papillary serous carcinoma.Gynecol Oncol 62：123−127, 1996.
14）Zanotti KM, et al：The use of paclotaxel and platinum-based chemotherapy in uterine papillary serous carcinoma. Gynecol Oncol 74：272−277, 1999.
15）伊藤潔ほか：癌治療における性維持の工夫．日本産婦人科学会 54, 1245−1255, 2002.

ELSEVIER

Controlled Clinical Trials 23 (2002) 55–57

Controlled Clinical Trials

Commentary

The issues to be considered in global drug development

Masahiro Takeuchi, Sc.D.

Division of Biostatistics, Department of Pharmaceutical Sciences, Kitasato University Graduate School, Tokyo, Japan

Drug review procedures and drug development strategies are changing rapidly due to "*The International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use*" (ICH), which was initiated in 1990 [1]. The ICH seeks to improve the efficiency of the development and review processes for promising new drugs by unifying necessary documentation and the associated formats for new drug applications (NDA) to regulatory agencies. In particular, the E5 guideline regarding ethnic factors in the acceptability of foreign clinical data has a significant impact on a new drug's development by allowing for the extrapolation of foreign clinical data as part of an NDA submission to the regulatory agency in a new region [2]. In consideration of intrinsic and extrinsic factors in new regions, a sponsor is required to conduct a small clinical trial called a "bridging study" in the new region to ensure that the profile of the drug derived from the foreign clinical data is applicable to a new region. The guideline provides two potential advantages: patients have quicker access to new therapies, and the sponsors can save money and time by avoiding a full-scale clinical trial in a new region when developing a drug.

The E5 guideline opens the door to simultaneous global drug development by specifying one global protocol for NDA submission in each region, as long as the sponsor has an appropriate bridging strategy. Many international pharmaceutical companies have responded by merging and establishing alliances in order to take advantage of global drug development possibilities and to speed global marketing of their products [3]. Regulatory agencies also have had to adjust to the realities of extrapolating foreign clinical data to their countries. The May 2001 symposium "APEC Network of Pharmaceutical Regulatory Science-APEC Joint Research Project on Bridging Study" was held in Taipei, Taiwan to discuss implementation of bridging studies among the regulatory agencies, academia and industries of APEC economies.

Globalization of drug development requires at least two conditions: a protocol to be reviewed by a regulatory agency before conducting a clinical trial in each region, and high

Corresponding author: Masahiro Takeuchi, Sc.D., Kitasato University Graduate School, School of Pharmaceutical Sciences, Division of Biostatistics, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan. Tel.: +81-3-5791-6322; fax: +81-3-3444-2546. E-mail address: takeuchim@pharm.kitasato-u.ac.jp

0197-2456/02/$—see front matter © 2002 Elsevier Science Inc. All rights reserved.
PII: S0197-2456(01)00198-2

quality of clinical data. The protocol review system in regulatory authorities play a very important role in avoiding unscientific and/or unethical clinical trials and ensuring the application of an equal standard of quality for clinical trials data. The U.S. Food and Drug Administration (FDA) directly consults with sponsors on protocol-related issues for the phase III trial at the end-of-phase II meeting. The Japanese regulatory authority, the Ministry of Health and Labor Welfare (MHLW), consults with sponsors via the Organization for Pharmaceutical Safety and Research (OPSR), a quasi-governmental organization, for protocol reviews and any related issues raised by reviewers and their consultants [4]. On the other hand, there does not exist a similar regulatory control over drug development [5]. Indeed protocol reviews by the research ethics committee at centers in the United Kingdom identified "substantial ethical concerns in the process of approving multicentre general practice pharmaceutical research" [6].

The paper by Keinonen et al. in this issue of *Controlled Clinical Trials* suggests that improvement of compliance with regulatory requirements would be enhanced by carefully prepared documentation from sponsors, who would then avoid unnecessary delay in conducting clincial trials. The Finnish drug regulatory agency, the National Agency for Medicines (NAM), requires a submission of notification of clinical trials after the ethics committee's approval has been obtained. Keinonen and others investigated the number and type of deficiencies in the 1174 clinical study notifications reviewed by the NAM in the sampled years 1992, 1994, 1996 and 1998. On average, 55% of the subject notifications were approved without modification, while 37% of the notifications had to be amended once and 5% amended twice before clinical studies were approved. Three percent of notifications were rejected.

In short, high quality study protocols were approved quickly, but the Keinonen paper raised two important issues. First, 43% of the applications did not receive approval from the NAM when first submitted, despite approval by ethics committees. The major reasons for the amendments were related to subject information and subject saftey issues because the ethics committee and the regulatory authority share overlapping responsibility for these areas, and it is not clear who has final decision-making authority. Implementation of clear operating procedures for protocol reviews is needed between the two parties to avoid ambiguity and unnecessary review time. In addition, the authors found deficiencies in study design and protocol issues in 15% of all cases rejected or sent back for amendment.

In the future, a high percentage of protocols will be submitted for global review, and regulatory authorities will have to evaluate methodological issues such as a choice of endpoint, study design issues (placebo control or active control), etc., so that the protocols are in accordance with their own extrinsic factors, especially focusing on medical practices.

The paper by Ono et al., also in this issue, identifies deficiencies detected from routine good clinical practice (GCP) audits by the OPSR in Japan. The authors examined OPSR findings from 125 new drug trials involving 331 hospital audits from April 1997 to March 2000. Five major categories of deficiencies identified include problems related to: the institutions, the investigators, case report form (CRF) entries, informed consent, the pharmacy and the archive. Deficient CRF entries (unreliability of data submitted to the MHLW) are the most problematic and are worthy of our attention. CRF deficiencies are closely related to two factors: Japanese medical practice (historical omission of concomitant drug use from CRFs)

and the clinical study environment (no allowance for on-site and timely monitoring by sponsors under the old GCP guideline, a lack of clinical research coordinators and research nurses, and no review of CRFs by sponsors before completion of a trial). Japanese routine GCP audits by the OPSR are targeted on clinical data and submitted documents. In contrast, audits by the U.S. FDA are mainly focused on the investigators. In Japan, sponsors are penalized for the submission of inadequate clinical data due to GCP violations by investigators at hospitals. This suggests that the implementation of the new guideline will not guarantee a high quality of clinical data in Japan unless the extrinsic factors (health care system and medical practice) are modified.

These two papers raise important questions about the conduct of good clinical trials from the regulatory point of view—how to ensure high quality clinical trials before their execution and how to ensure that trials will yield high quality clinical data after their execution. The solutions to these issues must be implemented in accordance with extrinsic factors (medical practice, clinical trial environment, and etc.) faced by each regulatory authority if we are to provide new therapies to patients globally in a short time.

References

[1] The International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) <<http://www.ifpma.org/ich.1.html>>.

[2] International Conference on Harmonisation of (ICH) Harmonised Tripartite Guideline. Ethnic Factors in the Acceptability of Foreign Clinical Data. Recommended for Adoption at Step 4 of the ICH Process on 5 February 1998 by the ICH Steering Committee.

[3] Lightfoot G, Getz K, Harwood F, et al. *Faster time to market. ACRP's white paper for future trends*. Association of Clinical Research Professionals, Washington; 1998.

[4] Fujiwara Y, Kobayashi K. Oncology drug clinical development & approval in Japan: The role fo the Pharmaceuticals and Medical Devices Evaluation Center (PMDEC). *Critical Reviews in Oncology/Hematology* in press.

[5] Tassignon JP. Preparing a clinical development plan. *GCP Journal* 2000;7:19–21.

[6] Wise P, Drury M. Pharmaceutical trials in general practice: the first 100 protocols. An audit by the clinical research ethics committee of the Royal College of General Practitioners. *BMJ* 1996;313:1245–1248.

British Journal of Cancer (2003) 88, 245–250
© 2003 Cancer Research UK All rights reserved 0007–0920/03 $25.00
www.bjcancer.com

Prognostic significance of positive peritoneal cytology in endometrial carcinoma confined to the uterus

T Kasamatsu*[,1], T Onda[1], N Katsumata[2], M Sawada[1], T Yamada[1], R Tsunematsu[1], K Ohmi[1], Y Sasajima[3] and Y Matsuno[3]

[1]Division of Gynecology, National Cancer Center Hospital, 5-1-1 Tsukuji, Chuo-ku, Tokyo 104-0045, Japan; [2]Department of Medical Oncology, National Cancer Center Hospital, 5-1-1 Tsukuji, Chuo-ku, Tokyo 104-0045, Japan; [3]Division of Diagnostic Pathology, National Cancer Center Hospital, 5-1-1 Tsukuji, Chuo-ku, Tokyo 104-0045, Japan

A retrospective analysis was performed to evaluate the prognostic significance of peritoneal cytology in patients with endometrial carcinoma limited to the uterus. A total of 280 patients with surgically staged endometrial carcinoma that was histologically confined to the uterus were examined clinicopathologically. The median length of follow-up was 62 (range, 12–135) months. All patients underwent hysterectomy and salpingo-oophorectomy with selective lymphadenectomy, and only three patients received adjuvant postoperative therapy. No preoperative adjuvant therapy was employed. In all, 48 patients (17%) had positive peritoneal cytology. The 5-year survival rate among patients with positive or negative peritoneal cytology was 91 or 95%, respectively, showing no significant difference (log-rank, $P=0.42$). The disease-free survival rate at 36 months was 90% among patients with positive cytology, compared with that of 94% among patients with negative cytology, and the difference was not significant (log-rank, $P=0.52$). Multivariate proportional hazards model revealed only histologic grade to be an independent prognostic factor of survival ($P=0.0003$, 95% CI 3.02 – 40.27) among the factors analysed (age, peritoneal cytology, and depth of myometrial invasion). Multivariate analysis revealed that histologic grade ($P=0.02$, 95% CI 1.21–9.92) was also the only independent prognostic factor of disease-free survival. We concluded that the presence of positive peritoneal cytology is not an independent prognostic factor in patients with endometrial carcinoma confined to the uterus, and adjuvant therapy does not appear to be beneficial in these patients.
British Journal of Cancer (2003) **88,** 245–250. doi:10.1038/sj.bjc.6600698 www.bjcancer.com
© 2003 Cancer Research UK

Keywords: endometrial carcinoma; peritoneal cytology

Malignant peritoneal cytology is recognised as an adverse prognostic factor in some gynaecologic malignancies. In ovarian cancer, there is a general consensus that postoperative adjuvant chemotherapy should be given to patients with positive peritoneal cytology even if the tumour is limited to the ovaries, that is, the International Federation of Gynecology and Obstetrics (FIGO) stage IC.

As for the positive prognostic value of peritoneal cytology in endometrial carcinoma confined to the uterus, there is still controversy, and conflicting results have appeared in the literature. Accordingly, there is no evidence as to the indication for and efficacy of adjuvant treatment in the case of positive peritoneal cytology. Several studies have reported the prognostic value of positive cytology, and proposed various modalities of adjuvant therapy, that is, multiagent chemotherapy, progestins, whole abdominal radiation, and intraperitoneal radioactive chromic phosphate (^{32}P) (McLellan *et al*, 1989; Lurain, 1992). On the other hand, investigators who found that malignant peritoneal cytology has poor prognostic value, found that adjuvant therapy was not beneficial (Yazigi *et al*, 1983; Konski *et al*, 1988; Lurain *et al*, 1989; Kadar *et al*, 1992). The question of the prognostic significance of malignant cytology in endometrial carcinoma confined to the uterus remains unanswered.

This retrospective clinicopathological study was undertaken to identify the prognostic significance of positive peritoneal cytology in endometrial carcinoma confined to the uterus.

*Correspondence: Dr T Kasamatsu; E-mail: takasama@ncc.go.jp
Received 15 July 2002; revised 3 October 2002; accepted 9 October 2002

PATIENTS AND METHODS

Patients

We reviewed the medical records and the cytologic and pathologic materials that had been obtained from 392 patients with surgically treated endometrial carcinoma at the Gynecology Division of the National Cancer Center Hospital, Tokyo, between 1990 and 1998. This study included patients who met the following criteria: the patient underwent primary surgery consisting of total abdominal hysterectomy and salpingo-oophorectomy with selective pelvic and/or para-aortic lymphadenectomy; the patient had no histologic evidence of extrauterine disease; peritoneal cytology was determined in a peritoneal washing obtained by laparotomy immediately upon entering the peritoneal cavity during primary surgery; and the patient had a histologic subtype of endometrioid adenocarcinoma or adenosquamous carcinoma. Patients with uncommon histologic subtypes (mucinous, serous, clear cell, and/or squamous cell carcinoma), and those who had other simultaneous primary malignancy were excluded. All of the

patients were surgically staged according to the FIGO staging system (1988), and histologic typing was evaluated according to the criteria of the WHO International Histologic Classification of Tumors.

Cytopathology

Cytological specimens were obtained by laparotomy upon entering the peritoneal cavity immediately before the primary surgery. Approximately 30 ml of sterile saline was instilled into the pelvis over the uterus, and then aspirated in the cul-de-sac. When a sufficient amount of ascites was present, the fluid was removed with a 20–30-ml syringe. The samples were subjected to cytocentrifugation onto slide glasses at 1700 rpm for 60 s at room temperature. The slides were then fixed in 95% ethanol, followed by Papanicolau stain, and alcian blue stain. Additional slides were stained immunocytochemically for CEA (Mochida, CEA010, Tokyo, Japan), and also for epithelial antigen defined by an antibody BerEP4 (DAKOPATTS, Glostrup, Denmark). Two to three cytotechnologists and cytopathologists independently examined all the slides to make a consensus diagnosis. A patient was considered to have positive peritoneal cytology if adenocarcinoma cells were detected regardless of the number of cancer cells. In this study, in cases where atypical cells were present but could not be definitively identified as cancer cells, the peritoneal cytology was considered to be negative.

Treatment

Our standard primary treatment for early-stage endometrial carcinoma was surgery consisting of extrafascial total abdominal simple hysterectomy, bilateral salpingo-oophorectomy and selective pelvic and/or para-aortic lymphadenectomy. In cases in which preoperative endometrial biopsy revealed histologic grade 1 tumour and no macroscopic myometrial invasion was found during the operation, lymphadenectomy was not performed. Para-aortic lymphadenectomy was performed if para-aortic node metastasis was diagnosed by pathologic sampling during the operation. Preoperative adjuvant therapy was not employed in any patient, and postoperative adjuvant therapy was not indicated for patients with limited disease.

The primary diagnosis of endometrial carcinoma was made by endometrial biopsy, which had been performed as an office procedure. Hysteroscopy was not performed prior to surgery. Before the surgery, the patients were examined by computed tomography and magnetic resonance imaging. Following the surgery, asymptomatic patients underwent pelvic examination, Pap smear, chest radiograph, ultrasonography, and/or determination of serial tumour markers every 4–6 months. Symptomatic patients underwent the appropriate examination where indicated.

Statistical methods

Survival and disease-free survival (DFS) curves were obtained by the Kaplan–Meier method and the survival curves were compared by nonparametric survival analysis (log-rank test). Variables that showed a significant association with survival or DFS, and peritoneal cytology were included in multivariate analysis based on the Cox-proportional hazards model. Patients who died of other causes were included as deaths in the survival analysis. Follow-up continued through 30 November, 2001. These statistical analyses were performed using the Statview statistical software package (version 5.0; SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient characteristics

In all, 280 patients met the study criteria, with a mean age of 56 years (range, 27–81 years) and a median length of follow-up of 62 months (range, 12–135 months). Of the patients, 112 who underwent surgery for endometrial carcinoma (mean age, 57 years) were excluded. Of these, 46 patients had extrauterine disease including stage III and IV. The remaining patients were excluded because of uncommon histologic subtype, other simultaneous malignancies, and/or inadequate cytologic materials. Of the 280 subjects, 48 patients (17%) had positive peritoneal cytology and 232 (83%) had negative cytology. The characteristics of the patients are summarised in Table 1. The histologic subtypes were the endometrioid type in 270 cases (96%) and the adenosquamous type in 10 cases (4%). The FIGO stage was as follows: 35 patients (12%) had stage IA disease, 123 (44%) had stage IB, 41 (15%) had stage IC, 5 (2%) had stage IIA, 28 (10%) had stage IIB, and 48 (17%) had stage IIIA. In total, 149 patients (53%) underwent simple hysterectomy and salpingo-oophorectomy with lymphadenectomy; 108 (39%) underwent simple hysterectomy and salpingo-oophorectomy without lymphadenectomy; and 23 (8%) underwent radical hysterectomy. Preoperative radiation therapy, chemotherapy, and progestin therapy were not administered to any patient. Only three patients received postoperative adjuvant therapy. These three patients with stage IIB carcinoma had deep cervical involvement, and external beam radiotherapy to the whole pelvis (total dose of 50 Gy) was administered postoperatively.

Survival

The cumulative survival was assessed in subgroups according to peritoneal cytology (positive or negative), age (over 60 years or 60 years and under), histologic grade (grade 1, grade 2, or grade 3),

Table 1 Patient characteristics

	Positive cytology n=48 (%)	Negative cytology n=232 (%)
Age (y)		
Over 60	12 (25)	76 (33)
60 or under	36 (75)	156 (67)
Histologic grade		
Grade 1	34 (81)	147 (63)
Grade 2	10 (17)	56 (24)
Grade 3	4 (2)	29 (13)
Myometrial invasion		
Absent	5 (10)	35 (15)
<1/3	20 (42)	106 (46)
1/3–2/3	11 (23)	52 (22)
>2/3	12 (25)	39 (17)
Cervical involvement		
Absent	34 (70)	198 (85)
Mucosal	7 (15)	6 (3)
Stromal	7 (15)	28 (12)
Lymph – vascular space invasion		
Absent	34 (71)	172 (74)
Present	14 (29)	60 (26)
Lymph node status		
Negative	32 (67)	140 (60)
Not resected	16 (33)	92 (40)

© 2003 Cancer Research UK

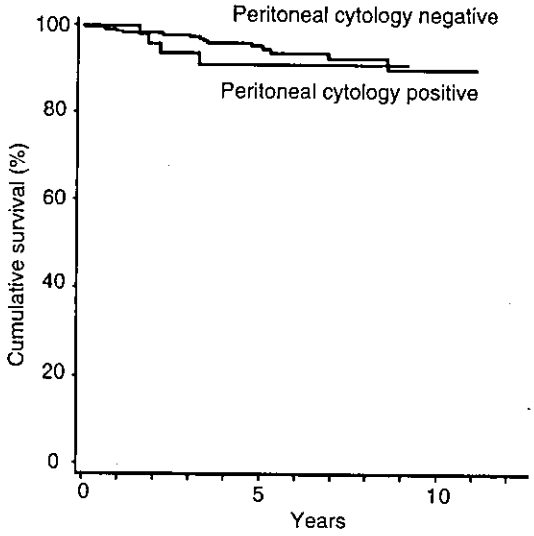

Figure 1 Survival of patients with endometrial carcinoma confined to the uterus according to the presence or absence of malignant peritoneal cytology.

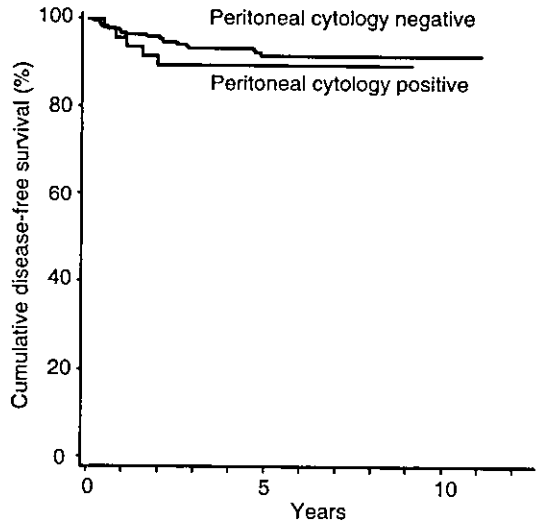

Figure 2 DFS in patients with endometrial carcinoma confined to the uterus according to the presence or absence of malignant peritoneal cytology.

Table 2 Univariate analysis and multivariate proportional hazards model for survival

	Univariate	Multivariate		
	P-value	Hazard ratio	95% CI[a]	*P*-value
Peritoneal cytology	0.42			
Positive		1.82	0.56–5.86	0.31
Age (y)	0.0045			
Over 60		2.50	0.93–6.71	0.06
Myometrial invasion	0.02			
<1/3		0.97	0.10–8.66	0.97
1/3–2/3		0.65	0.061–7.07	0.72
>2/3		1.27	0.13–12.35	0.83
Histologic grade	<0.0001			
Grade 2		3.28	0.81–13.21	0.09
Grade 3		11.02	3.02–40.27	0.0003

[a]95% confidence interval.

depth of myometrial invasion (absent, $<1/3$, $1/3-2/3$ or $>2/3$), cervical involvement (absent, mucosal, or stromal), lymph – vascular space invasion (absent or present), and lymph node status (not metastasised or not resected). The 5-year survival rate was 91% among the positive cytology group and 95% among the negative cytology group (Figure 1). There was no significant difference in survival between patients with positive or negative cytology (log-rank, $P=0.42$). There were no significant differences in the survival of patients in subgroups according to cervical involvement (log-rank, $P=0.89$), lymph – vascular space invasion (log-rank, $P=0.40$), and lymph node status (log-rank, $P=0.79$). Significant differences in survival were found among patients in subgroups according to age, myometrial invasion and histologic grade. Multivariate analysis of testing for differences in survival among the subgroups of cytology, age, depth of myometrial invasion, and histologic grade was performed. The proportional hazards model revealed that only histologic grade was an independent prognostic factor and positive cytology was not an independent adverse prognostic factor (Table 2).

Similarly, the DFS was assessed in the same subgroups. The DFS at 36 months was 90% among the patients with positive cytology, compared with 94% among the patients with negative cytology, and this difference was not significant (log-rank, $P=0.52$) (Figure 2). Univariate analysis also revealed no significant differences in the DFS of patients in subgroups according to lymph – vascular space invasion (log-rank, $P=0.29$), and lymph node status (log-rank, $P=0.60$). There were significant differences in the DFS of patients in subgroups according to age, myometrial invasion, histologic grade, and cervical involvement. Among these significant subgroups and the subgroup according to peritoneal cytology, the Cox-proportional hazards model showed that only histologic grade was an independent prognostic factor for DFS, and that positive cytology was not an independent factor (Table 3).

Prognosis and failure sites

Among the 280 patients, 14 patients (5%) suffered tumour recurrence. Table 4 presents the clinical characteristics of the recurrent patients. Peritoneal spread was found in only 20% (one out of five) of the patients with positive cytology who recurred, and the affected site was outside the peritoneal cavity in the remaining 13 patients.

DISCUSSION

In the past 20 years, over 50 reports on the significance of positive peritoneal cytology in endometrial carcinoma have been published, and many conflicting results have appeared in the literature. Based on studies that found that positive cytology is an independent adverse prognostic factor (Harouny *et al*, 1988; Mazurka *et al*, 1988; Brewington *et al*, 1989; Turner *et al*, 1989; Sutton, 1990; Morrow *et al*, 1991; Grigsby *et al*, 1992; Kadar *et al*, 1994; Descamps *et al*, 1997; Kashimura *et al*, 1997; Obermair *et al*, 2001), postoperative adjuvant therapy was recommended for patients with positive peritoneal cytology. Progestins, whole abdominal external radiation, intraperitoneal radioactive chromic phosphate (^{32}P), and multiagent chemotherapy have been proposed. The efficacy of these modalities for treating positive cytology in the absence of other evidence of extrauterine disease is not universally accepted (McLellan *et al*, 1989; Lurain, 1992). On the other hand, investigators who did not find that malignant peritoneal cytology is a significant prognostic factor found no benefit of adjuvant therapy in patients with positive cytology in the absence of other adverse prognostic factors (Yazigi *et al*, 1983;

© 2003 Cancer Research UK

Table 3 Univariate analysis and multivariate proportional hazards model for DFS

	Univariate	Multivariate		
	P-value	Hazard ratio	95% CI[a]	*P*-value
Peritoneal cytology	0.52			
Positive		0.83	0.24–2.88	0.77
Age (y)	0.005			
Over 60		2.23	0.93–5.32	0.06
Myometrial invasion	0.006			
< 1/3		1.94	0.23–16.04	0.53
1/3–2/3		2.16	0.23–19.85	0.49
>2/3		3.63	0.39–33.74	0.25
Histologic grade	<0.0001			
Grade 2		1.32	0.40–4.30	0.63
Grade 3		3.46	1.21–9.92	0.02
Cervical involvement	0.007			
Mucosal		3.47	0.86–14.01	0.07
Stromal		0.55	0.12–2.48	0.44

[a]95% confidence interval.

Hernandez *et al*, 1985; Konski *et al*, 1988; Hirai *et al*, 1989; Lurain *et al*, 1989; Grimshaw *et al*, 1990; Kadar *et al*, 1992; Kennedy *et al*, 1993; Ayhan *et al*, 1994; Ebina *et al*, 1997; Yalman *et al*, 2000). This discrepancy is probably because of the following: (1) the reported incidence of positive cytology was approximately 10% and the number of subjects was small; (2) the difference between the surgical stage and the clinical stage was not always distinguished; (3) various modalities of preoperative and/or postoperative therapies were used; (4) in the statistical analysis, multivariate analysis was not always employed; (5) the objectivity of the cytopathologic diagnosis was not always guaranteed; and (6) a prospective study has not been performed.

The prognosis of endometrial carcinoma appears to be good, and an overall 5-year survival rate of 76% can be achieved (Creasman *et al*, 2001) because the majority of patients with endometrial carcinoma have localised, low-grade disease at the time of primary treatment. Indeed, our data indicated that the 5-year survival rate of patients with endometrial carcinoma confined to the uterus was above 90% regardless of positive peritoneal cytology. Additionally, the Cox-proportional hazards model demonstrated that positive peritoneal cytology was not an independent adverse factor for survival and DFS. Although the number of patients in our study was not as large as that in some other studies, all patients were surgically staged and received no preoperative therapy. Only three patients (1%) were treated with postoperative adjuvant therapy. Considering the above facts, it is doubtful whether patients with no extrauterine disease except for positive peritoneal cytology require more aggressive therapy. As for the statistical power, it was difficult to evaluate the power calculation statistically because the number of statistical events was limited and our study was a retrospective one.

In the study of the Gynecologic Oncology Group (GOG) reported by Morrow *et al* (1991), 895 patients with clinical stage I or II (occult) carcinoma of the endometrium were analysed. In total, 29% of the patients with positive cytology developed recurrence compared with 10.5% of the cytology-negative patients, and a relation between malignant cytology and poor outcome was demonstrated by a multivariate model. This GOG study included patients with extrauterine disease, and 42.9% of the patients with no evidence of extrauterine disease received some form of postoperative radiotherapy. Turner *et al* (1989) demonstrated by multivariate analysis that positive cytology was a poor prognostic factor for both the 5-year survival rate (84 *vs* 96%) and progression-free interval (65% at 5 years *vs* 96%) among 567 patients with surgical stage I disease. In that study, 28 women (4.9%) had positive cytology, and the primary treatment was surgery alone for 90 patients (16%), surgery with preoperative adjuvant radiotherapy in 409 patients (72%), and surgery with postoperative adjuvant radiotherapy in 46 patients (8%). Preoperative radiotherapy may have affected the surgical stage and peritoneal cytology of many patients enrolled in that study.

Similarly, in many previous studies that found that positive peritoneal cytology had no prognostic significance, we found the same problems; for example, many patients received pre- or postoperative adjuvant therapy, or multivariate analysis was not employed. Grimshaw *et al* (1990) showed that there was no significant difference in the 5-year survival rate between patients with positive or negative cytology (80 *vs* 86%) among 305 surgical stage I patients. In that study, statistical significance was analysed with only the Fisher exact test. Kadar *et al* (1992) demonstrated that positive cytology did not influence survival if the disease was confined to the uterus using Cox's proportional hazards model. In that study, treatment variables included the use of adjunctive radiation therapy and the type of radiation therapy used, and 59% (159 out of 269) of the patients received radiation therapy. In the present study, no patient received preoperative therapy and only

Table 4 Clinical characteristics of 14 recurrent patients

Patient no.	Peritoneal cytology	Histologic grade	Depth of invasion	Cervical involvement	Initial failure sites	Time to recurrence (months)	Treatment	Status
1	Positive	1	>2/3	Mucosal	Nodes	24	Not done	DOD[b] (40)
2	Positive	1	< 1/3	Mucosal	Peritoneum	9	Chemo	AWD[c] (39)
3	Positive	2	< 1/3	Absent	Lung	19	Chemo	DOD (22)
4	Positive	3	>2/3	Mucosal	Lung	6	Chemo	DOD (19)
5	Positive	3	>2/3	Absent	Nodes, bone	24	RT[a]	DOD (26)
6	Negative	1	1/3–2/3	Absent	Vagina	4	RT	NED[d] (116)
7	Negative	1	1/3–2/3	Absent	Vagina	26	RT	NED (64)
8	Negative	1	>2/3	Stromal	Lung, vagina	4	RT, Chemo	NED (72)
9	Negative	1	Absent	Absent	Systemic	26	RT, Chemo	DOD (41)
10	Negative	1	>2/3	Stromal	Lung	13	Surgery	NED (57)
11	Negative	2	>2/3	Absent	Lung	33	Not done	DOD (42)
12	Negative	2	>2/3	Absent	Spleen	24	Surgery	AWD (47)
13	Negative	3	>2/3	Absent	Bone	11	Not done	DOD (13)
14	Negative	3	>2/3	Absent	Lung	31	Unknown	DOD (40)

[a]Radiation therapy; [b]Dead of disease; [c]Alive with disease; [d]No evidence of disease.

© 2003 Cancer Research UK

three (1%) of the 280 patients received postoperative adjuvant therapy.

Positive cytology was not an adverse prognostic factor in endometrial carcinoma limited to the uterus, and it is unknown from where these cancer cells were derived. Although there are insufficient data to reach a conclusion about the source of the cancer cells in peritoneal washings, the following mechanisms may be deduced from the literature (McLellan *et al*, 1989; Lurain, 1992): (1) result of transtubal transport; (2) direct extension of tumour through the myometrium; (3) lymphatic metastasis to the peritoneal cavity; and (4) reflection of multifocal peritoneal occult spread. The transtubal transport theory seems to be the most popular. Hirai *et al* (2001) demonstrated by using a tube that was inserted into the abdomen during the operation for cytologic analysis, that positive peritoneal cytology usually disappeared within a short period of time after the operation (within 14 days) in patients with limited disease in comparison to patients with adnexal metastasis. Additionally, as for the failure site in the present series, peritoneal spread was found in only 20% of the patients with positive cytology who recurred, and in the remaining patients, the affected site was outside the peritoneal cavity. Another study (Lurain *et al*, 1989) showed that 17% of patients with stage I disease who had positive cytology suffered recurrence, and only 20% of these recurrences were within the abdomen. The above-mentioned findings suggest that malignant cells obtained by peritoneal washing may not reflect the potential of peritoneal spread in a significant proportion of endometrial carcinoma cases unless other extrauterine disease is present.

In most studies including the present study, peritoneal cytology was analysed by conventional cytopathologic techniques and morphologic findings. Although cytopathologic findings including adequate sampling are essential for analysing the prognostic value of peritoneal cytology, evaluating the objectivity of cytopathologic diagnosis is difficult. The available data indicated that among 3091 reported cases with clinical stage I disease, the overall incidence of positive cytology was 11.4% (range, 2.9–29.8%) (McLellan *et al*, 1989). If the positive rate in a study is rather high, the possibility that reactive mesothelial cells were confused with malignant cells must be considered. If the positive rate in a study is too low, sampling error should be considered. Szpak *et al* (1981) demonstrated that the presence of abundant malignant cells (greater than 1000 cells per 100 ml sample) significantly shortened the time to recurrence. Yanoh *et al* (1999) proposed that the findings of endometrial adenocarcinoma cells exhibiting high cellularity, scalloped edge of cell clusters and isolated cells in peritoneal cytology could be regarded as a risk factor for intra-abdominal recurrence. Luo *et al* (2001) reported that analysis of peritoneal washings with conventional and immunocytochemical (MOC-31) staining improved the diagnosis of peritoneal cytology in endometrial carcinoma, and positive combined cytology was a prognostic factor. The results of research on these morphological findings have not yet been widely accepted, and will be worthy of consideration in the future.

Currently, we believe that the presence of positive peritoneal cytology is not an independent prognostic factor, and that it does not seem to reflect the potential of peritoneal spread in patients with endometrial carcinoma confined to the uterus. Adjuvant therapy such as chemotherapy, radiation therapy, or progestins does not appear to be beneficial in these patients at present. Nonetheless, further investigation and prospective multiinstitutional prospective analyses are needed.

REFERENCES

Ayhan A, Tuncer ZS, Tuncer R, Yuce K, Kucukali T (1994) Risk factors for recurrence in clinically early endometrial carcinoma: an analysis of 183 consecutive cases. *Eur J Obstet Gynecol Reprod Biol* 57: 167–170

Brewington KC, Hughes RR, Coleman S (1989) Peritoneal cytology as a prognostic indicator in endometrial carcinoma. *J Reprod Med* 34: 824–826

Creasman W, Odicino F, Maisonneuve P, Beller U, Benedet J, Heintz A, Ngan H, Sideri M, Pecorelli S (2001) Carcinoma of the corpus uteri. *J Epidemiol Biostat* 6: 47–86

Descamps P, Calais G, Moire C, Bertrand P, Castiel M, Le Floch O, Lansac J, Body G (1997) Predictors of distant recurrence in clinical stage I or II endometrial carcinoma treated by combination surgical and radiation therapy. *Gynecol Oncol* 64: 54–58

Ebina Y, Hareyama H, Sakuragh N, Yamamoto R, Furuya M, Sogame M, Fujino T, Makinoda S, Fujimoto S (1997) Peritoneal cytology and its prognostic value in endometrial carcinoma. *Int Surg* 82: 244–248

Grigsby PW, Perez CA, Kuten A, Simpson JR, Garcia DM, Camel HM, Kao MS, Galakatos AE (1992) Clinical stage I endometrial cancer: prognostic factors for local control and distant metastasis and implications of the new FIGO surgical staging system. *Int J Radiat Oncol Biol Phys* 22: 905–911

Grimshaw RN, Tupper WC, Fraser RC, Tompkins MG, Jeffrey JF (1990) Prognostic value of peritoneal cytology in endometrial carcinoma. *Gynecol Oncol* 36: 97–100

Harouny VR, Sutton GP, Clark SA, Geisler HE, Stehman FB, Ehrlich CE (1988) The importance of peritoneal cytology in endometrial carcinoma. *Obstet Gynecol* 72: 394–398

Hernandez E, Rosenshein NB, Dillon MB, Villar J (1985) Peritoneal cytology in stage I endometrial cancer. *J Natl Med Assoc* 77: 799–803

Hirai Y, Fujimoto I, Yamauchi K, Hasumi K, Masubuchi K, Sano Y (1989) Peritoneal fluid cytology and prognosis in patients with endometrial carcinoma. *Obstet Gynecol* 73: 335–338

Hirai Y, Takeshima N, Kato T, Hasumi K (2001) Malignant potential of positive peritoneal cytology in endometrial cancer. *Obstet Gynecol* 97: 725–728

Kadar N, Homesley HD, Malfetano JH (1992) Positive peritoneal cytology is an adverse factor in endometrial carcinoma only if there is other evidence of extrauterine disease. *Gynecol Oncol* 46: 145–149

Kadar N, Homesley HD, Malfetano JH (1994) Prognostic factors in surgical stage III and IV carcinoma of the endometrium. *Obstet Gynecol* 84: 983–986

Kashimura M, Sugihara K, Toki N, Matsuura Y, Kawagoe T, Kamura T, Kaku T, Tsuruchi N, Nakashima H, Sakai H (1997) The significance of peritoneal cytology in uterine cervix and endometrial cancer. *Gynecol Oncol* 67: 285–290

Kennedy AW, Webster KD, Nunez C, Bauer LJ (1993) Pelvic washings for cytologic analysis in endometrial adenocarcinoma. *J Reprod Med* 38: 637–642

Konski A, Poulter C, Keys H, Rubin P, Beecham J, Doane K (1988) Absence of prognostic significance, peritoneal dissemination and treatment advantage in endometrial cancer patients with positive peritoneal cytology. *Int J Radiat Oncol Biol Phys* 14: 49–55

Luo ML, Sakuragi N, Shimizu M, Seino K, Okamoto K, Kaneuchi M, Ebina Y, Okuyama K, Fujino T, Sagawa T, Fujimoto S (2001) Prognostic significance of combined conventional and immunocytochemical cytology for peritoneal washings in endometrial carcinoma. *Cancer* 93: 115–123

Lurain JR (1992) The significance of positive peritoneal cytology in endometrial cancer. *Gynecol Oncol* 46: 143–144

Lurain JR, Rumsey NK, Schink JC, Wallemark CB, Chmiel JS (1989) Prognostic significance of positive peritoneal cytology in clinical stage I adenocarcinoma of the endometrium. *Obstet Gynecol* 74: 175–179

Mazurka JL, Krepart GV, Lotocki RJ (1988) Prognostic significance of positive peritoneal cytology in endometrial carcinoma. *Am J Obstet Gynecol* 158: 303–306

McLellan R, Dillon MB, Currie JL, Rosenshein NB (1989) Peritoneal cytology in endometrial cancer: a review. *Obstet Gynecol Surv* 44: 711–719

© 2003 Cancer Research UK

Morrow CP, Bundy BN, Kurman RJ Creasman WT, Heller P, Homesley HD, Graham JE (1991) Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynaecologic Oncology Group study. *Gynecol Oncol* 40: 55–65

Obermair A, Geramou M, Tripcony L, Nicklin JL, Perrin L, Crandon AJ (2001) Peritoneal cytology: impact on disease-free survival in clinical stage I endometrioid adenocarcinoma of the uterus. *Cancer Lett* 164: 105–110

Sutton GP (1990) The significance of positive peritoneal cytology in endometrial cancer. *Oncology (Huntington)* 4: 21–26; discussion 30-32

Szpak CA, Creasman WT, Vollmer RT, Johnston WW (1981) Prognostic value of cytologic examination of peritoneal washings in patients with endometrial carcinoma. *Acta Cytol*, 25: 640–646

Turner DA, Gershenson DM, Atkinson N, Sneige N, Wharton AT (1989) The prognostic significance of peritoneal cytology for stage I endometrial cancer. *Obstet Gynecol* 74: 775–780

Yalman D, Ozsaran Z, Anacak Y, Celik OK, Ozkok S, Ozsaran A, Hanhan M, Haydaroglu A (2000) Postoperative radiotherapy in endometrial carcinoma: analysis of prognostic factors in 440 cases. *Eur J Gynaecol Oncol* 21: 311–315

Yanoh K, Takeshima N, Hirai Y, Minami A, Tsuzuku M, Toyoda N, Hasumi K (1999) Morphologic analyses of positive peritoneal cytology in endometrial carcinoma. *Acta Cytol* 43: 814–819

Yazigi R, Piver MS, Blumenson L (1983) Malignant peritoneal cytology as prognostic indicator in stage I endometrial cancer. *Obstet Gynecol* 62: 359–362

Gynaecology and Obstetrics

© 2003 Cancer Research UK

● 特 集 ●

婦人科がん診療の Latest Information

子宮体がん

勝俣 範之 山中 康弘 喜多川 亮

〔*Jpn J Cancer Chemother* 29(8): 1371-1376, *August*, 2002〕

要旨 化学療法剤の進歩により，子宮体がんに対してもある程度の奏効が得られるようになったが，依然として進行子宮体がんに対する化学療法は姑息的手段の域をでない。現状では進行子宮体がんに対する化学療法の効果は約40～60%である。併用化学療法としては，従来のCAP療法で31～56%，AP療法で33～81%の奏効率が得られたが，生存期間の改善は認められなかった。最近のpaclitaxel（TXL）を含んだ併用化学療法で，TAP療法(TXL 160 mg/m² 3 h，day 2，ADM 45 mg/m²，day 1，CDDP 50 mg/m² day 1)対AP療法(ADM 60 mg/m²，CDDP 50 mg/m²）比較試験で奏効率，生存率ともにTAP療法がAP療法より有意（p=0.024）に優っていた。taxane系薬剤は，今後子宮対がんの化学療法において中心的な薬剤となる可能性がある。

Latest Information of Therapeutic Approach for Endometrial Cancer: Noriyuki Katsumata, Yasuhiro Yamanaka and Ryo Kitagawa (*Dept. of Medical Oncology, National Cancer Center Hospital*)

Summary

The role of chemotherapy for metastatic endometrial carcinoma is palliation, although modest response can be achieved because of development of chemotherapy. The response rate is 31-56% of conventional CAP therapy and 33-81% of AP therapy. However these chemotherapeutic regimen did not prolong the survival. Recently, a randomized trial of TAP therapy (TXL 160 mg/m² 3h, day 2, ADM 45 mg/m², day 1, CDDP 50 mg/m² day 1) versus AP therapy (ADM 60 mg/m², CDDP 50 mg/m²) was reported. The response and survival of TAP is superior to that of AP. Taxane will be key drugs for chemotherapy of endometrial cancer in the future.

Key words: Endometrial cancer, Chemotherapy, Paclitaxel, Address request for reprints to: Dr. Noriyuki Katsumata, Department of Medical Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

I．進行子宮体がんに対する化学療法

化学療法剤の進歩により，子宮体がんに対してもある程度の奏効率が得られるようになったが，依然として進行子宮体がん（手術不能なIII期以上の進行がんや再発期のがん）に対する化学療法は姑息的手段（palliative therapy）の域をでない。現状では進行子宮体がんに対する化学療法の効果は約40～60%であり，効果の持続期間は3～6か月，生存期間の中央値は7～10か月とされている。

II．化学療法単剤

子宮体がんに対する単剤での化学療法の奏効率を表1[1]に示した。これをみると単剤での奏効率が20%を超えているのは，cisplatin(CDDP)，carboplatin (CBDCA)，doxorubicin (ADM)，epiru-

別刷請求先: 〒104-0045 東京都中央区築地5-1-1 * 国立がんセンター中央病院・腫瘍内科
勝俣 範之

表 1 単剤化学療法の成績

薬 剤	n	CR+PR	%
Cyclophosphamide	37	4	11
Ifosfamide	56	4+4	14
Cisplatin	63	3+10	21
Carboplatin	82	5+18	28
Doxorubicin	161	18+24	26
Epirubicin	27	2+5	26
Pirarubicin	28	2+0	7
Mitoxantrone	46	0+2	4
5-fluorouracil	34	7	21
Methotrexate	33	1+1	6
Vincristine	38	1+5	16
Vinblastine	48	1+3	8
Etoposide	29	0+1	3
Paclitaxel	47	6+11	36

bicin (EPI), 5-fluorouracil (5-FU), paclitaxel (TXL) の 6 剤のみである。TXL は卵巣がんに優れた成績を示しているが，子宮体がんにも単剤ではこれまでの化学療法のなかで最もよい奏効率を示している。GOG (Gynecologic Oncology Group) で行われた第II相試験[2]によると，28 名の再発・進行子宮体がん患者に TXL 250 mg/m²を 3 週間ごとに投与し，CR 4 名 (14%)，PR 6 名 (21%)，奏効率 36%を得ている。また，Lissoni ら[3]も 19 名の進行子宮体がん患者に TXL 175 mg/m 2 を 3 週間ごとに投与し，奏効率 37% (CR 2 名，PR 5 名) を報告している。

III. 併用化学療法 (ADM based chemotherapy)

併用化学療法の基本的な考え方は単独で有効とされ，異なる機序の化学療法剤を組み合わせ，その相乗効果によってより高い奏効率を得ようとするものである。奏効率を表 2 に示すが，単剤に比較して良好な成績が得られている。CAP 療法で 31～56%，AP 療法で 33～81%，CA 療法で 31～46%の奏効率が認められている。しかし，単アームだけの結果からは背景も異なるし，selection bias も存在することから一概に比較することは困難である。より高い evidence を供給するものはランダム化比較試験 (randomized controlled trial: RCT) の結果であるが，進行子宮体がんに対する RCT は多くは行われていない。GOG で行われた RCT が代表的なものであるが，ADM 単独 (60 mg/m²) と CA 療法 (ADM 60 mg/m²+cyclophosphamide: CPA 500 mg/m²) の RCT[17]では奏効率で 24% vs 32%，無増悪期間の中央値で 3.2 か月 vs 3.9 か月，生存期間の中央値でそれぞれ 6.7 か月 vs 7.3 か月であり，奏効率では有意差は認められず，生存期間でわずかに CA 群が優れていた。一方，ADM 単独 (60 mg/m²) と AP 療法 (ADM 60 mg/m²+CDDP 50 mg/m²) の RCT[18]では奏効率では 25% vs 42%と AP 療法が優れていたが，生存期間の中央値は 9.2 か月 vs 9.0 か月と差が認められなかった (GOG statistical report より)。

IV. TXL による化学療法

TXL は，イチイ科の植物 (学名: Taxus baccata) から抽出される 10-デアセチルバッカチン III を原料として合成された新規化学構造を有する抗悪性腫瘍剤であり，作用機序として微小管の蛋白重合を促進し，微小管の安定化・過剰形成を引き起こし，その結果細胞分裂を阻害して抗腫瘍効果を示すと考えられ，既存の抗悪性腫瘍剤とはその作用機序が異なる。卵巣がんで優れた効果を発揮し，わが国でもすでに卵巣がんに対して認可されている薬剤である。単剤化学療法の項でも示し

表 2 併用化学療法の成績

療法名		n	CR+PR	%
CAP療法				
Edmonson[4]		16	0+5	31
Burke[5]		87	12+27	45
Turbow[6]		19	2+7	47
Dunton[7]		17	3+5	47
Hancock[8]		18	5+5	56
AP療法				
Seltzer[9]		9	1+2	33
Trope[10]		20	2+10	60
Barrett[11]		30	6+12	60
Pasmantier[12]		16	6+7	81
CA療法				
Seski[13]		26	0+8	31
Thigpen[14]		105	15+19	32
Muggia[15]		11	3+2	45
Campora[16]		13	1+5	46
Randomized study				
Thigpen[17]	ADM	90	22	24
	vs			
	CA	105	34	32
Thigpen[18]	ADM	150	38	25
	vs			
	AP	131	55	42

たように，子宮体がんに対してもTXLの効果が注目を浴びている。併用化学療法としては，プラチナ製剤やEPI，ADMと併用した結果が報告されている[19-21]。2000年ASCOでAP（ADM 60 mg/m²，CDDP 80 mg/m²）vs AT（ADM 60 mg/m²，TXL 175 mg/m² 3 h）の比較試験（GOG 163）が報告された（図1）[22]。314名が登録され，奏効率AP 40%，AT 43%であり，TTPでもAP 7.2か月，AT 6.0か月と，ATはAPを優ることができなかった。GOGはCDDP，ADMとTXLの3剤（TAP療法）を組み合わせた第I相試験を施行し[23]，推奨投与量をTXL 160 mg/m²，ADM 45 mg/m²，CDDP 60 mg/m²とし，2002年ASCOでAP（ADM 60 mg/m²，CDDP 50 mg/m²）vs TAP（TXL 160 mg/m² 3 h，day 2，ADM 45 mg/m²，day 1，CDDP 50 mg/m² day 1）の比較試験（GOG 177）を報告した（図2）[24]。266名が登録され，奏効率AP群33%，TAP群57%とTAPが優り，1年生存率でもAP群50%，TAP群59%とTAPがAPより有意（p=0.024）に優っていた。この結果は，進行子宮体がんの比較試験で生存率で有意差が初めて認められた試験として注目される。この試験はTAP群で，TXLがday 2に投与されること，grade 3神経毒性が多かったこと（12%），G-CSFが予防的に投与されていることから，実地診療に取り入れるのには困難な点も多いが，現在，EORTCが同様のデザインでGOG 177の追試を開始している（図3）ので，その結果が期待されるところである。また，同じtaxane系薬剤のdocetaxel phase II studyが現在わが国で進行中である。今後の子宮体がんの化学療法はtaxaneがkey drugとなってくる可能性が高いと考えられる。

V. 術後補助療法としての化学療法

術後補助療法としての化学療法は再発のhigh

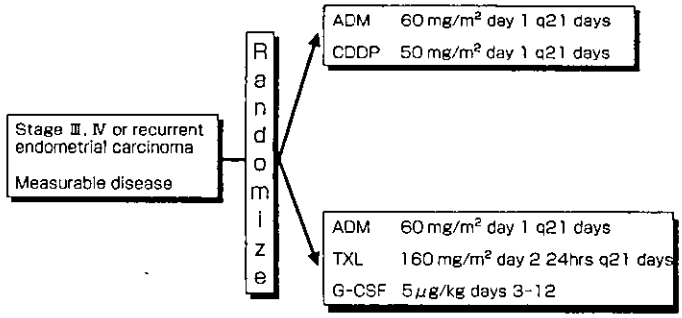

図 1 GOG 163

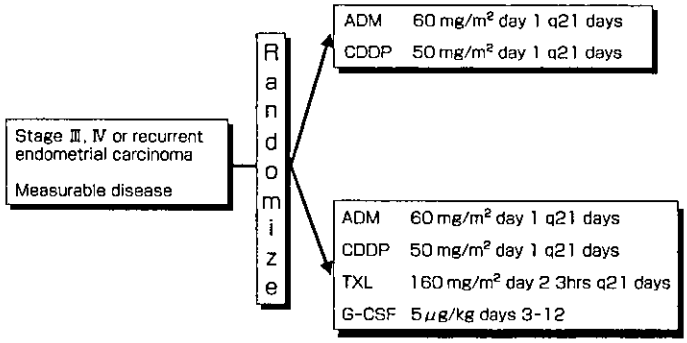

図 2 GOG 177

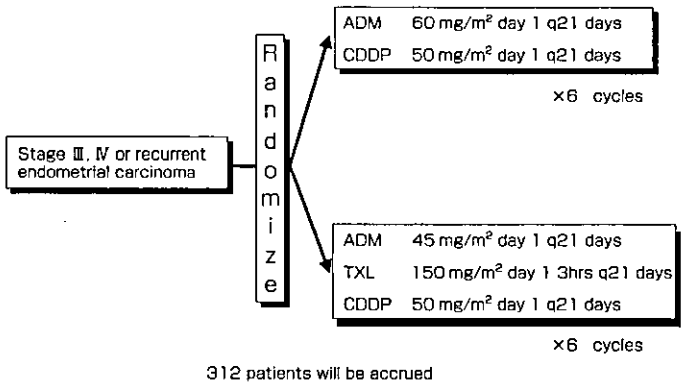

図 3 EORTC 55984

risk 例（骨盤，または傍大動脈リンパ節転移のある症例や，筋層浸潤が深い症例など）が対象となると考えられるが，現在のところ術後化学療法の有用性は確認されていない。単アームの試験では Onda ら[25]がリンパ節転移陽性 30 症例に CAP 療法（CPA 600 mg/m²，ADM 40 mg/m²，CDDP 75 mg/m²）3 コース後，放射線治療を行い，5 年生存率 84%の好成績を得ている。

RCT では GOG で術後リンパ節転移が陽性，50%以上の筋層浸潤，頸部・附属器浸潤のあった症例を対象として，放射線治療後に ADM 60 mg/m²を 3 週間ごとに総投与量 500 mg/m²まで投与

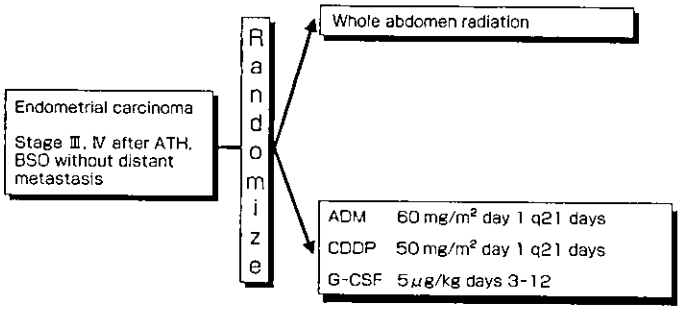

図 4 GOG 122

する群（92名）と，無治療で経過観察する群（89名）とのRCTを行った[26]。この試験は症例登録率が極めて悪く，9年間で181例しか登録されず，不適格症例も43例と多く，ADM群に割り付けられた患者のうち25名は実際にADMの投与がなされなかったことが問題とされ，かなり統計学的検出力が弱まってしまった。実際に再発率，生存率ともに両群で差は認められなかったが，検出力が弱かったため，この試験だけでは化学療法が本当に無効なのかどうかは証明することはできないと考えられる。GOGではStage III，IV期でATH＋BSO後に全骨盤照射を行う群と化学療法（ADM＋CDDP）を行う群の比較試験を行った（図4）。この試験はすでに症例登録を終了し，経過観察期間を経て数年以内に発表されると思われる。この結果により術後放射線治療がよいのか，化学療法を行うことがよいのか，臨床的な疑問に回答をしてくれると思われる。術後化学療法のレジメンに関しても今後はTXLなどのnew drugを取り入れた研究が今後なされていくであろうと思われる。

文 献

1) Hoskins WJ, Perez CA and Young RC: Corpus: Epithelial tumors in principles and practice of gynecologic oncology, 2 nd ed, Lippincott-Raven, Philadelphia, 1997, pp 859-896.
2) Ball HG, Blessing JA, Lentz SS, *et al*: A phase II trial of paclitaxel in patients with advanced or recurrent adenocarcinoma of the endometrium: a Gynecologic Oncology Group study. *Gynecol Oncol* **62**: 278-81, 1996.
3) Lissoni A, Zanetta G, Losa G, *et al*: Phase II study of paclitaxel as salvage treatment in advanced endometrial cancer. *Ann Oncol* **7**: 861-863, 1996.
4) Edmonson JH, Krook JE, Hilton JF, *et al*: Randomized phase II studies of cisplatin and a combination of cyclophosphamide-doxorubicin-cisplatin (CAP) in patients with progestin-refractory advanced endometrial carcinoma. *Gynecol Oncol* **28**: 20-24, 1987.
5) Burke TW, Stringer CA, Morris M, *et al*: Prospective treatment of advanced or recurrent endometrial carcinoma with cisplatin, doxorubicin, and cyclophosphamide. *Gynecol Oncol* **40**: 264-267, 1991.
6) Turbow MM, Ballon SC, Sikic BI, *et al*: Cisplatin, doxorubicin, and cyclophosphamide chemotherapy for advanced endometrial carcinoma. *Cancer Treat Rep* **69**: 465-467, 1985.
7) Dunton CJ, Pfeifer SM, Braitman LE, *et al*: Treatment of advanced and recurrent endometrial cancer with cisplatin, doxorubicin, and cyclophosphamide. *Gynecol Oncol* **41**: 113-116, 1991.
8) Hancock KC, Freedman RS, Edwards CL, *et al*: Use of cisplatin, doxorubicin, and cyclophosphamide to treat advanced and recurrent adenocarcinoma of the endometrium. *Cancer Treat Rep* **70**: 789-791, 1986.
9) Seltzer V, Vogl SE and Kaplan BH: Adriamycin and cis-diamminedichloroplatinum in the treatment of metastatic endometrial adenocarcinoma. *Gynecol Oncol* **19**: 308-313, 1984.
10) Trope C, Johnsson JE, Simonsen E, *et al*: Treatment of recurrent endometrial adenocar-

cinoma with a combination of doxorubicin and cisplatin. *Am J Obstet Gynecol* **149**: 379-381, 1984.
11) Barrett RJ, Blessing JA, Homesley HD, *et al*: Circadian-timed combination doxorubicin-cisplatin chemotherapy for advanced endometrial carcinoma. A phase II study of the Gynecologic Oncology Group. *Am J Clin Oncol* **16**: 494-496, 1993.
12) Pasmantier MW, Coleman M, Silver RT, *et al*: Treatment of advanced endometrial carcinoma with doxorubicin and cisplatin: Effects on both untreated and previously treated patients. *Cancer Treat Rep* **69**: 539-542, 1985.
13) Seski JC, Edwards CL, Gershenson DM, *et al*: Doxorubicin and cyclophosphamide chemotherapy for disseminated endometrial cancer. *Obstetrics Gynecol* **58**: 88-91, 1981.
14) Thigpen JT, Blessing JA, DiSaia P, *et al*: A randomized comparison of adriamycin with or without cyclophosphamide in the treatment of advanced or recurrent endometrial cancer. *Proc ASCO* (abstr): 115, 1985.
15) Muggia FM, Chia G, Reed LJ, *et al*: Doxorubicin-cyclophosphamide: effective chemotherapy for advanced endometrial adenocarcinoma. *Am J Obstetrics Gynecol* **128**: 314-319, 1977.
16) Campora E, Vidali A, Mammoliti S, *et al*: Treatment of advanced or recurrent adenocarcinoma of the endometrium with doxorubicin and cyclophosphamide. *Eur J Gynaecol Oncol* **11**: 181-183, 1990.
17) Thigpen JT, Blessing JA, DiSaia PJ, *et al*: A randomized comparison of doxorubicin alone versus doxorubicin plus cyclophosphamide in the management of advanced or recurrent endometrial carcinoma: A Gynecologic Oncology Group study. *J Clin Oncol* **12**: 1408-1414, 1994.
18) Thigpen JT, Blessing JA, Homesley H, *et al*: Phase III study of doxorubicin with/without cisplatin in advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group (GOG) study. *Proc ASCO* (abstr): 261, 1993.
19) Lissoni A, Gabriele A, Gorga G, *et al*: Cisplatin, epirubicin and paclitaxel-containing chemotherapy in uterine adenocarcinoma. *Ann Oncol* **8**: 969-972, 1997.
20) Markman M, Kennedy A, Webster K, *et al*: Carboplatin plus paclitaxel in the treatment of gynecologic malignancies: the Cleveland Clinic experience. *Semin Oncol* **24**: S 15-26-S 15-29, 1997.
21) Price FV, Edwards RP, Kelley JL, *et al*: A trial of outpatient paclitaxel and carboplatin for advanced, recurrent, and histologic high-risk endometrial carcinoma: preliminary report. *Semin Oncol* **24**: S 15-78-S 15-82, 1997.
22) Fleming GF, Brunetto VL, Bentley R, *et al*: Randomized trial of doxorubicin (DOX) plus cisplatin (CIS) versus DOX plus paclitaxel (TAX) plus granulocyte conony-stimulating factor in patients with advanced or recurrent endometrial cancer: a report on Gynecologic Oncology Group Protocol # 163. *Proc ASCO* (abstr): 1498, 2000.
23) Fleming GF, Flowler JM, Waggoner SE, *et al*: Phase I trial of escalating doses of paclitaxel combined with fixed doses of cisplatin and doxorubicin in advanced endometrial cancer and other gynecologic malignancies: a Gynecologic Oncology Group study. *J Clin Oncol* **19**(4): 1021-1029, 2001.
24) Fleming GF, Brunetto VL, Mundt AJ, *et al*: Randomized trial of doxorubicin (DOX) plus cisplatin (CIS) versus DOX plus CIS plus paclitaxel in patients with advanced or recurrent endometrial carcinoma: A Gynecogic Oncology Group (GOG) trial. *Proc ASCO* (abstr): 807, 2002.
25) Onda T, Yoshikawa H, Mizutani K, *et al*: Treatment of node-positive endometrial cancer with complete node dissection, chemotherapy and radiation therapy. *Br J Cancer* **75**: 1836-1841, 1997.
26) Morrow CP, Bundy BN, Homesley HD, *et al*: Doxorubicin as an adjuvant following surgery and radiation therapy in patients with high-risk endometrial carcinoma, stage I and occult stage II: a Gynecologic Oncology Group Study. *Gynecol Oncol* **36**: 166-171, 1990.

特集　セーフティーマネージメント

外来化学療法におけるセーフティーマネージメント

勝俣範之[*1]　渡辺　亨[*1]　安藤正志[*1]　清水千佳子[*1]
喜多川　亮[*1]　山中康弘[*1]　徳永伸也[*1]　河野　勤[*1]
大江裕一郎[*1]

Safety Management of Ambulatory Chemotherapy: Katsumata N, Watanabe T, Andoh M, Shimizu C, Kitagawa R, Yamanaka Y, Tokunaga S, Kohno T, One Y (Department of Medical Oncology, National Cancer Center Hospital)

Safety management of chemotherapy is important because mistake of management of chemotherapy may cause patients to death. Practical essential matters of safety management of ambulatory chemotherapy are as follows, ambulatory treatment center, computerization of chemotherapy ordering, medical specialists (medical oncologist, oncology nurse and clinical pharmacist), risk management care, and evidence-based supportive care.

Key words: Ambulatory chemotherapy, Safety management, Medical oncologist, Oncology nurse, Clinical pharmacist

Jpn J Breast Cancer 17(5): 418～422, 2002

はじめに

がん化学療法は投与方法を誤るとその副作用により場合によっては患者の生命を脅かしてしまう危険があり，安全性の確保に十分に注意する必要がある．外来化学療法を行う際のセーフティーマネージメントのポイントは，ハード面では，専門ブース，オーダーのコンピュータ化，専門職種（腫瘍内科医，専門看護師，専門薬剤師）によるマネージメント，リスクマネージメントケアの実践，ソフト面では，EBM（Evidence-based Medicine）に基づいた治療，適切な支持療法などの確立が重要である．本稿では国立がんセンター中央病院での実際の外来化学療法の現状を紹介するとともに，セーフティーマネージメントについて解説していくこととする．

1. 専門ブース（通院治療センター）の設置

外来化学療法を実施するためには，通院治療センターの整備は必須である．国立がんセンター中央病院の通院治療センターは1979年に開設されて以来，通院治療を施行してきた．新棟に移転（1999年）してからは，32床(ベッド19，チェア13)，看護師7名の体制で1日平均で70名の外来化学療法を行っている（図1)．通院治療センターは化学療法の実施だけでなく，一般点滴，検査・処置なども行う．化学療法の業務はそのうち約3分の2を占める（図2)．2001年度は18,159名が外来治療を受けその数は年々増えてきている（図3）ためブース拡大が望まれている．疾患別化学療法患者の割合（図4）では，乳がんが一番多く，2000年度は4,599名（1日平均17.7名）に外来化学療法を行っている．乳がんの化学療法は

*1 国立がんセンター中央病院腫瘍内科