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Treatment and Prognosis of Brain Metastases From Gynecological Cancers

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Abstract

Brain metastases from gynecological cancers were retrospectively investigated in 18 patients who were treated between 1985 and 2006. Six patients received surgical resection followed by radiotherapy, and 12 patients received only radiotherapy. The median survival for all patients was 4.1 months (range 0.7–48.2 months), and the actuarial survival rates were 11% at both 12 months and 24 months. Univariate analysis showed that treatment modality, extracranial disease status, total radiation dose, number of brain metastases, and Karnofsky performance status (KPS) all had statistically significant impacts on survival. Two patients survived for more than 2 years, and both had single brain metastasis, inactive extracranial disease, 90–100% KPS, and were treated with surgical resection followed by radiotherapy. Improvements in neurological symptoms were observed in 10 of the 12 patients treated with palliative radiotherapy, with median duration of 3.1 months (range 1.5–4.5 months). The prognoses for patients with brain metastases from gynecological cancers were generally poor, although selected patients may survive longer with intensive brain tumor treatment. Palliative radiotherapy was effective in improving the quality of the remaining life for patients with unfavorable prognoses.

Key words: radiation therapy, brain metastasis, gynecological neoplasm, uterine cervical cancer, endometrial cancer, ovarian cancer

Introduction

Brain metastases develop in approximately 10–30% of cancer patients and the prognoses of these patients have historically been poor. The most common primary tumors responsible for brain metastases are lung, breast, and unknown primary tumors, and melanoma.[41] In contrast, brain metastases originating from gynecological malignancies are extremely rare, with the exception of choriocarcinoma, and the incidence of brain metastases in clinical series for all gynecological cancers is approximately 1%.[36,41]

Recently, advances in neuroimaging, such as computed tomography (CT) and magnetic resonance (MR) imaging, have allowed careful monitoring of cancer patients, which together with the increased survival of patients, has led to more frequent and earlier detection of brain metastases. Therefore, clinical reports of brain metastases from gynecological cancers have increased gradually.[19,32]

The present study evaluated our experience with brain metastases from gynecological cancers to identify the treatments and factors that influence the prognosis of these patients.

Materials and Methods

A retrospective review of the medical records of 2729 patients with gynecological cancer treated at the University of the Ryukyus Hospital between 1985 and 2006 identified 18 patients (0.7%) with documented brain metastases from gynecological cancers. The brain metastases were diagnosed by CT with contrast medium or, more recently, CT and/or MR imaging. Six of the 18 patients had histo-

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logical confirmation of the diagnosis after undergoing surgical resection of the brain lesion. All patients underwent primary medical evaluation including detailed history, review of symptoms, and physical examination before a treatment plan was formulated, and follow-up information was obtained from the patients' records or from communications with the patients or their physicians.

Six of the 18 patients were treated with surgical resection followed by radiotherapy (S + RT group), and the remaining 12 patients were treated with radiotherapy (RT group). Radiotherapy used a 4-MV, 6-MV, or 10-MV linear accelerator to administer daily fractions of 2–3 Gy 5 days per week. Stereotactic radiosurgery was not applied. Fifteen patients received whole brain radiotherapy (WBRT) of 5–50 Gy (median dose 30 Gy), and three patients received WBRT (40 Gy in 20 fractions) followed by local boost using the appropriate technique (dose range 50–60 Gy). The doses were 30–60 Gy (median 50 Gy) for the S + RT group and 5–50 Gy (median 30 Gy) for the RT group. Corticosteroids in individualized doses were given during radiotherapy. Three patients then received systemic chemotherapy using cisplatin with or without 5-fluorouracil or a combination of adriamycin and cyclophosphamide.

In this study, statistical analysis examined the following potential prognostic factors affecting survival: age (<65 years or ≥65 years), Karnofsky performance status (KPS; ≥70% or <70%), primary histology (squamous cell carcinoma or others), initial International Federation of Gynecology and Obstetrics (FIGO) stage, extracranial disease status (active or inactive), number of brain metastases (single or multiple), greatest dimension of brain metastases (<4 cm or ≥4 cm), interval between diagnosis of primary tumor and brain metastases (<2 years or ≥2 years), treatment modality for brain metastases (S + RT or RT), total radiation dose (<50 Gy or ≥50 Gy), primary tumor site (ovary or others), and use of chemotherapy (yes or no). Patients were considered to have no evidence of active extracranial disease if there were no metastases outside the brain and the primary tumor was controlled. The term *controlled primary tumor* referred to a primary tumor in complete remission after surgical resection, radical radiotherapy/radiochemotherapy, or a combination of these treatments.

A recursive partitioning analysis (RPA) of three Radiation Therapy Oncology Group (RTOG) studies used the following classification: Class 1, patients with KPS ≥70, age <65 years with controlled primary disease and no evidence of extracranial metastases; Class 3, patients with KPS <70; and Class 2, all remaining patients who did not fit into Class 1 or 3.[14] To ascertain whether this scoring system is also applicable to patients with brain metastases from gynecological cancers, our patients were grouped into these three classes for analysis.

All data were updated to December 2006. Overall survival rate was calculated according to the Kaplan-Meier method[18] and survival was measured from the date of diagnosis of brain metastases until the date of last follow up or until death. Differences between groups were estimated using the log-rank test.[27] A probability level of 0.05 was chosen for statistical significance. Statistical analysis was performed using the SPSS software package (version 11.0; SPSS Inc., Chicago, Ill., U.S.A.).

Results

Table 1 indicates the incidence rates of brain metastases from gynecological cancers according to the primary tumor site. In total, 0.7% of the patients with gynecological malignancies treated in our institutions developed brain metastases. The incidence of brain metastases from ovarian cancer (2.1%) was higher than those from other primaries (0.4–0.7%).

The patients were aged 38–74 years (median 53

Table 1 Incidences and median survival of patients with brain metastases (BM) from gynecological cancers

Primary site	Previous reports			Current study		
	Reference No.	Incidences of BM (%)	Median survivals (mos)	Patients with BM/total patients	Incidence of BM (%)	Median survival (range) (mos)
Ovary	4, 10–19	0.3–2.2	1.3–19.5	7/335	2.1	7.3 (0.9–48.2)
Uterine cervix	20–24	0.4–1.2	3.0–7.8	7/1716	0.4	2.8 (0.7–28.4)
Uterine corpus	25–30	0.3–0.9	1.0–5.3	4/556	0.7	4.3 (3.1–4.9)
All sites included*	31	1.8	7.3	18/2729	0.7	4.1 (0.7–48.2)

*Other sites include vagina, vulva, and fallopian tube.

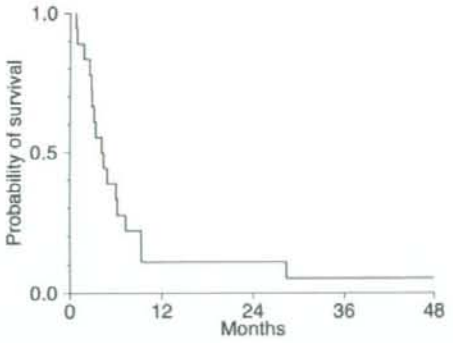

Fig. 1 Actuarial overall survival curves for the 18 patients with brain metastases from gynecological cancers.

years) at the time of initial diagnosis of gynecological cancers. All patients had histologic confirmation of their primary lesion. Seven patients had squamous cell carcinoma, and 11 had adenocarcinoma. At the time of initial primary treatment, 11 patients had clinical FIGO stage I–II tumors, and seven had stage III–IV tumors.

The patients were aged 42–74 years (median 55 years) at the time brain metastases appeared, and KPS was 30–100% (median 60%). The signs and symptoms were headache in eight patients, motor weakness in seven, seizures in two, and cerebellar dysfunction, disorientation, speech disturbance, and diplopia in one each. All patients underwent chest radiography, chest CT, and abdominal CT. Sixteen of the 18 patients underwent radionucleotide bone scintigraphy. Extracranial disease status was active in 14 patients; three had recurrent extracranial metastases, and 11 had both uncontrolled primary tumor and extracranial metastases. The interval between the diagnoses of primary tumor and appearance of brain metastases was 0–78 months (median 16 months). Five patients had single brain metastasis, and six had brain metastases with largest dimension ≥4 cm.

The median survival was 4.1 months (range 0.7–48.2 months). The actuarial overall survival rates were 11% at both 12 months and 24 months (Fig. 1). The median survival was 9.3 months (range 4.9–48.2 months) for patients in the S + RT group and 2.9 months (range 0.7–6.2 months) for patients in the RT group. Univariate analysis showed that treatment modality, KPS, extracranial disease status, number of brain metastases, and total radiation dose all had statistically significant impacts on survival (Table 2). No significant differences in survival were seen with respect to other factors.

Table 2 Univariate analysis of various potential prognostic factors for survival in patients with brain metastases (BM) from gynecological cancers

Variable	No. of patients	Overall survival at 1 yr	p Value
Treatment modality			
S+RT	6	33	0.0005
RT	12	0	
Extracranial disease			
active	14	0	0.0011
inactive	4	25	
Total radiation dose			
<50 Gy	14	0	0.013
≥50 Gy	4	50	
No. of BM			
single	5	40	0.019
multiple	13	0	
KPS			
<70%	10	0	0.021
≥70%	8	25	
Primary tumor site			
ovary	7	14	0.065
others	11	9	
Primary tumor histology			
squamous cell carcinoma	7	14	0.25
adenocarcinoma	11	9	
Age			
<65 yrs	12	17	0.29
≥65 yrs	6	0	
Use of chemotherapy			
yes	3	27	0.40
no	15	7	
Initial FIGO stage			
stages I–II	11	9	0.42
stages III–IV	7	14	
Interval from primary Dx to BM Dx			
<2 yrs	12	8	0.60
≥2 yrs	6	17	
Greatest dimension of BM			
<4 cm	12	8	0.83
≥4 cm	6	17	

Dx: diagnosis, FIGO: International Federation of Gynecology and Obstetrics, KPS: Karnofsky performance status, RT: radiotherapy, S: surgery.

Two patients survived for more than 2 years. Both patients had single brain metastasis, inactive extracranial disease, 90–100% KPS, and were treated with S + RT. No late complications, such as mental deterioration, were observed during follow up in either patient. One patient died of recurrent brain metastasis after 48.2 months, and the other patient died of recurrent extracranial metastasis after 28.4 months.

The median survival was 22.4 months for the three patients in RPA class I, 4.9 months for the six patients in RPA class II, and 2.8 months for the nine patients in RPA class III. There were statistically significant differences in survival between these groups ($p = 0.001$).

Ten of the 12 patients treated with palliative radiotherapy showed improvements in neurological symptoms, including headache, motor weakness, seizures, and cerebellar dysfunction, with duration of 1.5–4.5 months (median 3.1 months). Six of these 12 patients died of brain metastases accompanied by deterioration of neurological symptoms, and the other six patients died of pneumonia without deterioration of neurological symptoms.

Discussion

In the current study, 0.7% of the patients with gynecological cancers treated in our institutions developed brain metastases. The incidence of brain metastases from ovarian cancer (2.1%) was higher than those from other primaries (0.4–0.7%). This is consistent with other studies with the reported rates of 0.3–2.2% for ovarian cancer and 0.6–0.9% for other cancers.[1,6-13,16,17,19-21,23-26,31,34,35,37,38] Clearly, brain metastases from gynecological malignancies are rare, but recent reports suggest an increasing incidence of brain metastases, especially in patients with ovarian cancer.[19,32] The use of effective combination chemotherapy, especially regimens containing cisplatin for ovarian cancer, may increase survival, providing time for occult brain metastases to become overt. Another explanation for the possible increase in brain metastases is the availability of better imaging techniques for diagnosis.[32] Further studies are required to monitor whether incidence rates among these patients will continue to increase in the future.

The primary mechanism of spread to the brain is dissemination to the lungs, then to the brain via the pulmonary vasculature.[41] Brain metastases from gynecological cancers are usually found in association with widely disseminated disease.[1,19,29,31] Our study found that 14 of 18 patients had active extracranial diseases at diagnosis of brain metastases. These results indicate that patients with brain metastases usually have disseminated systemic diseases at the time of clinical appearance of brain metastases.

Brain metastases are a major detrimental event in the natural history of most malignancies. In the majority of patients, the treatment of brain metastases is a palliative measure, because the primary disease is often advanced, and the general condition of these patients often is poor. Despite numerous studies designed to improve treatment outcome, the median survival is only 3–6 months.[4,33,41] In the present study, the median survival was 4.1 months, and actuarial survival was 11% at both 12 months and 24 months. Therefore, our results also indicated that the prognoses of patients with brain metastases from gynecological cancers were generally poor, like those from non-gynecological sites.

Achieving local tumor control in the brain is now known to improve the survival of selected patients. Two randomized trials that excluded patients with multiple brain metastases showed that surgical resection plus radiotherapy was significantly better than only radiotherapy.[30,39] Stereotactic radiosurgery also provided local control equivalent to surgery and facilitated the treatment of patients with surgically inaccessible or multiple lesions.[2,5] In our study, both patients who survived for more than 2 years were treated with S + RT. Both patients had inactive extracranial disease, and also had KPS of 90–100%. The median survival for the three patients in RPA class I (all treated with S + RT) was 22.4 months, which was comparable with the 14.8 months in the previous S + RT study.[3] The median survival of 4.9 months for the six patients in RPA class II (2 treated with S + RT) and that of 2.8 months for the nine patients in class III (1 treated with S + RT) were comparable with the 3.8–4.2 months and 2.3 months, respectively, in the previous studies.[14,15] Brain metastases from ovarian cancer are responsive to chemotherapy.[28,40] Therefore, multimodal treatments may provide better results in selected patients who may profit from effective local tumor control in the brain, than in all patients with brain metastases from gynecological cancers.

The present study also indicated that for patients with unfavorable prognoses, palliative radiotherapy was effective in improving the quality of remaining life, as in patients with other primaries. WBRT is effective for the palliation of symptoms resulting from intracranial metastases.[22] The result of the first two RTOG metastatic brain studies, which mainly incorporated patients with metastatic lung and breast cancer, suggested that the administration of WBRT could improve neurologic function in 50% of patients, and 70% to 80% of patients spent their remaining lives in an improved or stable neurologic state.[4] Symptomatic response was obtained in 23 of 32 patients with brain metastases from ovarian cancer.[11] All of 15 ovarian cancer patients with brain metastases who received radiotherapy showed improvement in neurological symptoms.[34] The present study, which included ovarian cancer, uterine cervical cancer, and uterine corpus cancer, observed improvements of neurological function in 10 of 18

patients after treatment.

The present study indicates that the prognoses for patients with brain metastases from gynecological cancers are generally poor, although selected patients may survive longer with intensive brain tumor treatment. Palliative radiotherapy is recommended for patients with unfavorable prognoses. However, this retrospective study included a relatively small number of patients, so further studies are necessary to confirm our results.

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Commentary

In a scientifically sound, retrospective study of 2729 patients with gynecological cancer, the authors report on 18 patients who developed brain metastases. This subgroup had a remarkably poor prognosis (median survival about 4 months) despite treatment modalities (i.e., surgical resection and radiation or radiation alone). In the 2 patients who survived for more than 2 years, both had a single brain metastasis, inactive extracranial disease, and high Karnofsky performance scores. The authors noted that palliative radiotherapy was effective in improving quality of remaining life in patients with an unfavorable prognosis.

We recommend that the authors and readers consider the use of intraoperative radiation implants in select patients with single brain metastasis for local tumor control.[1] *In our experience, we believe that this radiation protocol is preferred versus whole brain radiation therapy for reducing the potential for long-term radiation induced toxicity. As the authors report on their experience for a small group of patients with brain metastases from gynecological cancer, they recommend further study.*

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This paper is a retrospective review from records of 18 cases with brain metastases from gynecological cancers. The authors demonstrated that treatment modality, extracranial disease status, total radiation dose, number of brain metastases, and KPS had significant impacts on survival. These factors have been shown both in other and their own material to be significant prognostic factors for brain metastasis. These new data could be helpful for our clinical practice in the future. However, because brain metastases from gynecological cancers are very rare, more randomized trials are needed in the future.

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各委員会報告事項

GCIG委員会

GCIG委員会委員長
寒河江悟

まず最初に，2年前に私がASCOで発表させていただきましたJGOG2033の論文が，ようやく『Gynecologic Oncology』に採用されました．JGOGとしては初めてのRCTの論文ですので皆さんで喜んでいただければと思います．年明けぐらいまでには『Gynecologic Oncology』に掲載されると思いますので，ぜひご覧いただければと思います．

現在のGCIG委員会の委員は6名で構成されており，本日の「Annual Report」にありますように，年2回GCIG総会があります．春は6月の4日・5日にASCO，シカゴで開催されまして，先ほどお話ありましたJGOG3017のトライアルをアメリカ，カナダ，イギリスの各GCIGのメンバーに説明会を別に設けて，登録をできるだけ早くしていただけるように依頼を行いました．

続きまして，9月には，state-of-the-art scienceということで，子宮頸がんのコンセンサス・ミーティングがワシントンで開かれました．そこにGCIG委員会を代表して藤原先生，子宮頸がん委員会から佐々木寛先生の両先生に出ていただきまして，治療というよりも診断の方の話が主だったかと思いますが，いずれ皆さまに情報が提供されるかと思います．

今回は，10月28日にありました秋のGCIG総会の内容を抜粋して皆さんにお伝えします．

まず，2年に1回GCIGはチェアマンが代わりまして，今回は，イギリスMRCの代表でありますHenry Kitchenerが，来年度からチェアマンになるということが決定されました．次に，新GCIG会員として，皆さんよくご存じのSWOG（アメリカの臨床試験グループ）と韓国のKGOGがプロビジョナル・メンバーとして，今回の会議で承認されました．Phase III臨床試験などが1つでも正確に走るようなことになりますと，正確な意味でのフルメンバーとして昇格されるかと思います．

皆さんご存じのように，ウェブ上でGCIG活動はどんどん世界に発信しておりますが，今までアメリカNCIのCTEPのホームページの中に付録として入っていましたが，今度IGCSのホームページの中に，このGCIGのホームページが移るということが今回決まりました．まだ正確には動いておりませんが，近々IGCSのホームページを経由してGCIGの活動がご覧になれるというような状況であります．

さてGCIG秋季総会ですが，最初，エグゼクティブ・ボードに私が出まして，いろいろ議論がありました．FIGO進行期分類が改定になるというお話を去年からお話しさせていただいているんですけども一向に進んでおりません．実は，米子の婦人科腫瘍学会に，そのチェアマンであります Pecorelli先生がイタリアから来られますので，皆さんでぜひお話を聞かせていただければと思っております．実はGCIG会議でも全然話が進展していないことに皆さんいらいらしておられました．

来年2008年のスケジュールは6月シカゴにてASCOの時と，リバプールでイギリスとオランダが合同の婦人科がん会議を開きますので，その時11月に会議を開くということになっています．

これがエグゼクティブ・ボードの内容で，さら

に午後からはワーキンググループに，頸がん，卵巣がん，体がんという形で，それぞれ分担して会議に参加させていただきました．内容に関してましては，もうすこし時間を頂いて，いつも「GCIGだより」というのを皆さんに発信しておりますので，「Annual Report」とは別に「GCIGだより」も正確に皆さんにJGOGホームページにアップさせていただきますので，ぜひご覧いただければと思います．エグゼクティブ・ボードは1日半のGCIG総会中に実に3回会議を開きます．このワーキンググループの前に一度，さらに終りましたらそのサマリーをエグゼクティブ・ボードで，また20人ぐらい集まって討論されます．

その後にいつもGCIG会議参加者は皆さん一堂に会して食事をします．私はたまたまIGCS会議にも出席予定があり，BlackwellがIGCSのofficial journalである『Int J Gynecol Cancer』の出版社ですが，種々の問題から，LWWという会社に変更になるという一大事が起こりました．この会議が夜中の11時まで経過し大変な議論でありました．

次の日にはGCIGの全体会議に大体今回は70人ほどの全員が集まりまして，それぞれのメンバーグループが，今どんな臨床試験に取り組んでいるのかということを報告し，さらに内容を討論し，具体的にそれぞれのグループが，どの臨床試験に参加できるのかどうか，その参加に際しての問題点は何なのかということを議論しました．

卵巣がんに関しましては藤原先生からいずれ報告がありますが，子宮体がんに関しましては，分子標的薬のCCI779を使用する試験とPORTEC IIIという術後にRT単独とシスプラチン併用のCCRT＋adjuvant chemotherapy Taxol/CBDCAという比較試験が現在動いており，皆さんが注目しておりました．

頸がんに関しましては，state-of-the-art science報告がされましたし，運営委員会20施設に保存的手術のアンケート調査がありまして，それをGCIGに報告させていただきましたが，そのサマリーも近々出てくるとのことであります．

今回から，この総会の後半に，debateのセッションが1時間ほど設けられ，最近話題の子宮体がんの手術に骨盤リンパ節郭清や傍大動脈リンパ節郭清が実際に必要なのかどうか，どのような症例に必要で，どのような症例に必要でないのかということをdebate形式で発表がありました．最近イギリスやスカンジナビアから出たデータではあまり必要がないのではという趣旨の発表がありました．

最後に，さらなるエグゼクティブ・ボード会議がありまして，実はチェアマンのほかに，今回新しい提案ですが，co-chairを決め1年ずつずれて2年の任期で活動していただこうということが決まりました．また2004年の卵巣がんコンセンサス会議が開かれ，2005年に『Annal Oncol』に20ページ程の報告がなされましたが，そこで積み残した課題を来年か再来年にもう1度卵巣がんコンセンサス会議を開こうと提案がなされ，スペインが早速開催地に名乗りを上げていました．それから，FIGO進行期改定に関しては，Michael Quinnも委員ですので，Pecorelli先生にアプローチをするとのこと，米子にPecorelli先生が来られるということもありまして，皆さんでぜひお聞きしたいと考えております．

以上が，今回のベルリンでのGCIG秋季総会の報告とさせていただきますが，また『GCIGだより第3号』というのを作りますので，ぜひそれもご覧いただければと思います．

Current Organ Topics:

Gynecologic Cancer
婦人科 癌

Ⅲ．子宮体癌における化学療法

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〔*Jpn J Cancer Chemother* 35(2): 218-223, *February*, 2008〕

はじめに

2006年11月28，29日英国のマンチェスターにて子宮体癌に関する国際会議が開催され，分子メカニズム，治療法，今後の臨床試験のあり方について，早期がん，進行がん，稀な組織型（明細胞，漿液性腺癌など）の治療，translational researchなどを対象に討議された[1]。これは英国のNCRI，米国のNCI-US，さらに国際的臨床試験グループであるGCIGの共同開催であり，その内容から現在世界の専門家はどのような理解のもとに今後の臨床研究を考えているのかを整理し，特に化学療法に焦点を当てて解説してみたい。

1．原則は手術療法

子宮体癌の治療は，あくまで手術療法の役割が中心である。そこで術後の再発危険因子を理解することが最も重要であり，子宮体癌の術後管理をいかに正確に行うかに直結する課題である。再発危険因子は子宮内因子と子宮外因子に分けられ[2]，表1のごとく多くの因子が存在し，それぞれがFIGOの進行期分類で反映されている[3]。

表1 子宮体癌の予後因子

Uterine Factors	Extrauterine Factors
Histology	Adnexal Metastases
Grade	Intraperitoneal Spread
Myometrial Invasion	Peritoneal Cytology
Cervical-Isthmus Extension	Pelvic Node Metastases
Lymph-Vascular Invasion	Paraortic Node Metastases

昨今はこれらの危険因子を危険度の程度別に，low，intermediate，high riskなどとグループ分けされ詳細に検討されている（図1）。そしてこれらが種々の治療法の選択に欠かせない指針となっている。従って，正確な術後進行期の決定がその症例の予後を語るもっとも正確な手段であることは議論の余地がない。

こと手術に関しては，単純子宮全摘術とは異なり，広汎子宮全摘術を子宮体癌で行うことが骨盤内や腟断端への再発を減らすとされ，リンパ節への再発転移をも低くするものとされてきたが，早期であるⅠ期症例への広汎子宮全摘術を支持する証拠は何もない。この手術は明らかな頸管浸潤を伴ったⅡb期症例に限られるべきである[4]。リンパ節郭清の効用は疾患の進行期を決め，そうすることで予後を推測し術後療法の必要性を決めることである。しかしリンパ節を摘出すること自体が治療的意義があるか否かは今日もっとも議論のあるところである[5]。2007年米国でのASCO総会にてASTEC試験の報告[6]があり，二段階の無作為化試験によりTAH & BSO後にリンパ節郭清を行うかどうかと，病理学的に再発高危険群であるが肉眼的に完全に摘出された症例には，放射線の外照射を行うか否かにより，生存期間が比較された（図2）。全生存期間は治療法で差はなかったが，無再発期間はリンパ節郭清のない群で，行った群より優っていた。彼らは多数の症例での成績であり骨盤リンパ節郭清は特に術後療法の存在下では生存期間を延長するものではないと結論した。リンパ節郭清群には無再

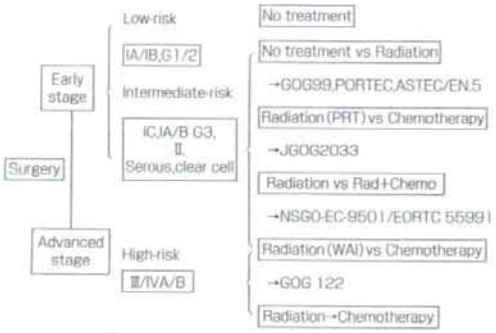

図1 リスク別術後療法のシェーマ

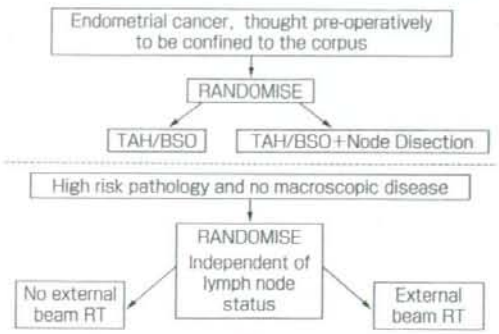

図2 ASTEC臨床試験 ASCO2007

表 2 Radiotherapy versus Chemotherapy in endometrial cancers JGOG2033[11], Italian Study[12] and GOG122[13]

	JGOG2033* (Susumu N, 2007)	Italian Study (Maggi R, 2006)	GOG 122 (Randall ME, 2006)
Regimen RT	Pelvic	Pelvic±PA	WAI
CT	CAP	CAP	AP
Number of Patients	385	340	396
Disease Stage	Ⅰc, 61%; Ⅱ, 14% Ⅲ, 25%	Ⅰ, 26.5%; Ⅱ, 9% Ⅲ, 64.5%	Ⅲ, 73%; Ⅳ, 27%
5-year PFS RT	84	63	38
CT	82	63	50**
5-year OS RT	86	69	42
CT	87	66	55**

*In press **Adjusted for stage, $p<0.01$

発期間の短い傾向が確認され，さらに術後の放射線治療によるリンパ浮腫の増大という危険性もあると強調した。日本の婦人科がん化学療法研究機構JGOGは子宮体癌に関するアンケート調査[7]を行い，子宮の摘出方法やリンパ節郭清には国内的に種々の方法が用いられていることを報告し，子宮摘出法は単純とPiver Ⅱ型（いわゆる準広汎）が1/3ずつで，あとは進行期を考慮して子宮を摘出するというものであった。さらなる広汎手術を行うか否かの質問では，30%のみが行うと回答し，決して子宮を広範囲に摘出することが予後改善につながるとは考えていない。また傍大動脈リンパ節郭清については，いつも行うのが13%しかなく，81%は腫瘍関連因子の存在で選択的に行っていたし，6%の施設では全然行っていなかった。この場合の腫瘍関連因子は傍大動脈リンパ節転移，分化度3，筋層浸潤1/2以上，組織型が漿液性・明細胞，骨盤リンパ節転移などが20%以上の因子であった。結論としては子宮体癌の手術術式はいまだ標準化されておらず[4]，子宮全摘術，両側付属器摘出術，骨盤リンパ節郭清，選択的傍大動脈リンパ節郭清が日本で行われている子宮体癌の今日的術式であることが判明した。子宮体癌における手術に関する三大問題点は，子宮の摘出術式すなわち単純か広汎か，リンパ節郭清か生検か，傍大動脈リンパ節の扱いである。これらの種々の術式の治療的意義を決定づける臨床試験を大々的に行うことは，子宮体癌における術式の標準化に最も寄与するであろうと結論つけられた。

2．術後療法

次に骨盤放射線療法，すなわち外照射と腔内照射は，これまで何十年も広く子宮体癌治療の基本であった。特に進行期不明な症例の術後療法の場合やintermediateやhighリスク症例やリンパ節転移症例など，さらに摘出不能な骨盤内進展症例などには放射線療法が標準であった。Intermediateリスク症例に対する放射線療法は三つの無作為化臨床試験が存在し，the Norwegian trial[8]，PORTEC Ⅰ[9]，GOG99[10]である。これらはすべて骨盤内再発の減少には寄与するが，最終生存には寄与しなかった。さらにGOG試験ではリンパ節郭清後の骨盤照射群に合併症の明らかな増加を認めた。

術後療法としての放射線療法と化学療法を直接比較した日本の臨床試験は2005年にASCOで報告されたが，Ⅰc期からⅢ期までの385例が登録され，CAP療法と骨盤放射線療法が比較された[11]が，これまでに放射線療法と化学療法の直接比較は三つの臨床試験（表2）しか存在せず，JGOG2033[11]，Italian Study[12]，GOG122[13]である。これらを比較すると，JGOG2033では完全手術で筋層浸潤1/2以上症例でⅠcからⅢc期まで登録され，類内膜腺癌385例が放射線療法とCAP化学療法の無作為化比較試験で検討された。一次評価項目は全生存期間であり，二次的には無再発期間と副作用であった。両群は年齢，閉経，合併症，術式，進行期などに有意な差はなく，Ⅰc期61%，Ⅱ期14%，Ⅲa期13%，Ⅲc期12%であった。約74%がⅠcからⅡb期までであった。結論としては385例での両群の比較では無再発や全生存期間には全く差はなく，サブ解析でintermediateリスクでもさらに再発危険度の低い群190例では両群に予後の差はないが再発危険度の高い群（Ⅱ期からⅢa期など）では放射線治療群より有意に化学療法群で予後良好であった[11]。

Italian Studyのhighリスク子宮体癌症例に対する放射線療法と化学療法CAP療法の比較であり，Ⅰc/Ⅱ期G3とⅢ期症例345例が登録され，化学療法はcisplatin（CDDP）50 mg/m^2，doxorubicin（DXR）45 mg/m^2，cyclophosphamide（CPA）600 mg/m^{2}を4週毎に5サイクルであり，放射線療法は外照射（45～50 Gy週5日治療）であった。両群で全生存期間に差はなかったが放射線療法は骨盤内再発を遅らせ，化学療法は遠隔転移を遅らせた[12]。

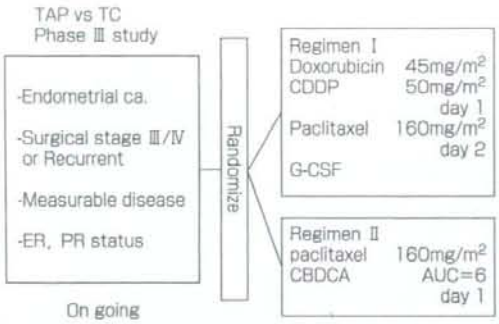

図 3 GOG209[15]

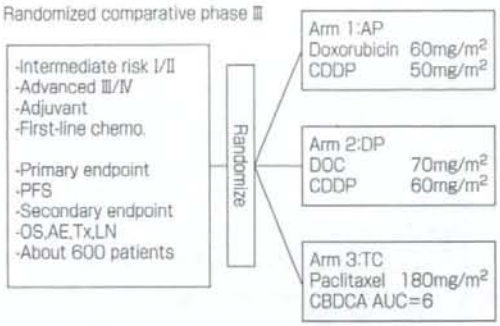

図 4 Ongoing Phase Ⅲ JGOG2043[18]

進行子宮体癌での放射線療法と化学療法の比較はGOG122研究があり2004年にASCOで報告され2006年に論文化された。全腹腔内照射とAP化学療法の比較であり，396例のⅢ期Ⅳ期症例が登録され，予後の比較では神経障害や心毒性がより強く出たが，明らかに放射線療法より化学療法が良好であった。この研究結果はその後の治療法に多大なインパクトを与え，標準であった放射線療法から選択肢としての「化学療法」の時代へのあけぼののようであった[13]。

3．子宮体癌における化学療法

それまでの化学療法は進行・再発子宮体癌症例の中でも肥満症例や前回放射線療法症例，高齢者などに限られていた。化学療法の既往なし症例では20%程度の効果が期待できた。たとえばDXR/epirubicin（EPI），paclitaxel（PTX）/docetaxel（DOC），さらにCDDP/carboplatin（CBDCA）などの併用療法である。AP療法は長い間唯一の標準化学療法であったが，GOGがAP対AP+PTX（TAP）の比較試験GOG177を行った[14]。既往の化学療法なしで測定可能病変がある進行・再発子宮体癌症例を対象に，AP療法とAP+PTX（G-CSF補助）療法の比較を行った。結果としてTAP療法が生存率の優越性を認めたが副作用が重症であり死亡症例も認められた。そこで現在より副作用の少ないPTX/CBDCA療法が第Ⅱ相試験で検討され60%を越える奏効率が得られている。そこで現在GOGではTAP療法vsTC療法の比較をⅡ期からⅣ期子宮体癌症例を対象に登録を進めている（GOG209）（図3）。本試験にはJGOGの中のGOG Japanを通じて日本人女性も登録が行われており，今後の研究成果が期待されている。

これらの状況の中，JGOGは最近さらに子宮体癌における化学療法のアンケート調査を行い，国内的にもPTX/Platinum（CBDCA）が最も汎用されている化学療法であることが示されている[15]。JGOGでは数年前からTaxane系薬剤とプラチナ系薬剤の併用の中で最も有効な薬剤の検討も始めており，JGOG2041では，DOC/CDDP，DOC/CBDCA，PTX/CBDCAの3種類の併用療法を30例ずつ登録し，2004年に登録終了し現在予後解析を待っているところである。中間解析ではPTX/CDDPが最も神経毒性が強かった[16]。3併用療法の中で副作用の出現頻度は異なり，DOC/CDDPでは消化器毒性がより強く発現し，DOC/CBDCAやPTX/CBDCAでは貧血や血小板減少がより高頻度であった。さらに1年経過での奏効率はDOC/CDDPで51.7%であり，PTX/CBDCAは60.0%であったが，DOC/CBDCAでは48.3%とやや低かった。

このJGOG2041に引き続き，現在国内では臨床第Ⅲ相試験JGOG2043（図4）が進行中である[17]。Ⅰc期，G2/G3，Ⅱ/Ⅲ期子宮体癌の術後治療として3種類の併用化学療法が無作為化され，登録が進んでいる。化学療法の内容はJGOG2041で評価されたDOC/CDDPとPTX/CBDCAであり，対照治療がこれまでの基本であるAP療法の3治療法である。現在各群200例の目標に対しやや登録が遅れているがすでに計100例以上の登録がなされており，今後の登録を期待しつつ最終成績に注目しているところである。一次評価項目は無再発期間であり，二次評価項目は全生存期間，副作用，治療内容，リンパ節転移などである。本研究は，GOG209と並んで，子宮体癌に対するTaxane系薬剤とプラチナ系薬剤の併用療法のなかで何が最も効果的なのかを決定することにもなり極めて重要である。

4．ホルモン療法

ホルモン療法は過去40年以上にわたって進行・再発子宮体癌症例に効果があるとされてきた。単剤プロゲステロン製剤（GOG48やGOG81[18]）ではPR陽性腫瘍やG1腫瘍に20%の奏効率があるとされた。またプロゲステロン製剤とタモキシフェンの併用療法（GOG119 and GOG153[19]）は30%内外の臨床効果があるとされた。さらに昨今ではaromatase inhibitors，anastrozoleやle-

trozole などの臨床効果が検討されたが極めて限定的であった。またホルモン剤のこれまでの臨床試験を総合的に判定した Meta-analysis では，プロゲステロン製剤は初回治療の補助療法としての臨床効果は有効でないと結論されている[20]。それでも子宮体癌症例に対する保存的治療法への応用も本邦では検討され，早期子宮体癌や内膜増殖症の症例に MPA を投与する第Ⅱ相試験がこのほど発表された[21]。40歳未満のⅠa期子宮体癌症例28例と異型内膜増殖症17例の合計45例が登録され，MPA 600 mg を低用量アスピリンとともに26週間連続投与された。病理学的 CR は子宮体癌症例の55%，異型増殖症の82%で観察され，全体で pCR 率は67%にのぼった。これらの症例群では経過観察3年間で12例にその後妊娠が確認され，7例で無事出産にこぎつけている。従って子宮体癌や異型増殖症に対する妊孕能温存高用量 MPA 療法の有用性はこの前方視的研究により証明された。しかし有効例においても実質的再発率の高さから厳重な経過観察が必要であることが結論つけられた。

5．分子標的療法

現在，生物学的治療法が種々の分子標的に対して多くの臨床試験が実施されている。子宮体癌においても同様であり，大きな流れとして二つの方向性が現存する。すなわちひとつは子宮体癌で43%に発現している PTEN に対する治療法である。PTEN 機能の欠損が AKT を増加させ，mTOR を増加させる。原発腫瘍では mTOR が70%で増加しており，再発腫瘍でも50%で増加しており，この mTOR 抑制剤は治療に極めて重要である．たとえば RAD001[22]，CCI-779（NCIC）などが報告されており，CCI-779 は16例中5例の PR が得られ31%の奏効率を報告している[23]。もうひとつは EGFR に対する治療法である。EGFR は子宮体癌の60～80%（とくに漿液性）に発現しており，EGFR 標的治療はこれまで多くの薬剤が開発され，たとえば Iressa（GOG 229-C），Herceptin（GOG 181b），and Erlotinib などであり，OSI-774（NCIC）では7%の奏効率が報告されている。

6．ASCO2007 における NSGO/EORTC 臨床試験

以上のごとく，子宮体癌に対する化学療法にも種々の薬剤の試みが現在進行中である。そのような状況の中，本年の ASCO で子宮体癌の治療法に関して極めて重要な報告がなされた。それは NSGO/EORTC の共同研究であり，早期 high リスク子宮体癌症例の術後療法として，放射線単独療法か，それに化学療法を併用するか否かの無作為化臨床試験（図5）である[24]。登録の基準は，子宮全摘術と両側付属器摘出術の後に手術進行期Ⅰ期とⅡ期，さらに腹腔内細胞診陽性のⅢa期，骨盤リンパ節転移要請のⅢc期を対象にしており，さらに漿液性，明

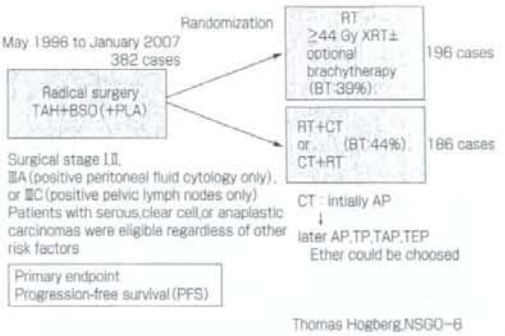

図5　NSGO and EORTC at ASCO 2007.[31]

細胞，未分化癌などは他のリスク因子の有無にかかわらず登録対象としている。症例は放射線療法群と放射線療法と化学療法の併用群に無作為に分けられ，化学療法はこれまで有効とされた AP，TP，TAP，または TEP 療法などが含まれている。一次評価項目は無再発期間であり，90%の症例が進行期Ⅰ期に属したが，67%は類内膜腺癌 G3，明細胞，漿液性がんであった。これまでの試験の結果は無再発期間で両群間に明らかに差があり，放射線療法に化学療法が併用された群で有意に予後良好であった。演者らはこれらのデータより，併用群に割り振られた症例の27%が化学療法を受けなかったり，一部しか受けなかったにもかかわらず，両治療法の併用が早期子宮体癌で微小転移を認める high リスクの症例には術後療法として両治療法の併用が放射線療法単独より有用であると結論した。NSGO/EORTC では現在今後の臨床試験としてまずは術後に化学療法を行い，その後に放射線療法を行うか否かの臨床試験を企画中である。ということは，NSGO/EORTC では早期子宮体癌の術後療法の標準は化学療法であり，高 intermediate リスク症例である微小転移を認める可能性がある症例がまさに適応であると伝えている。

最後に，2006年英国で開催された子宮体癌に関するコンセンサス国際会議のまとめとして，

A）今後早期子宮体癌に対する術後療法としては化学療法の重要性を十分に認識しておかなければならない。今後将来の方向性として注目される臨床試験は以下のごとくである。

1）現在登録中の PORTEC Ⅲ臨床試験

これは骨盤放射線療法と化学療法併用放射線療法＋地固め化学療法の比較である。対象はⅠb期Ⅰc期 G3，Ⅱ期 G3，Ⅲa期またはⅡc期の類内膜腺癌，さらにⅠb期からⅢc期までの明細胞か漿液性癌である。化学療法併用放射線療法は7日目と22日目に CDDP 50 mg/m^{2}を併用し，地固めに PTX/CBDCA（175/AUC5）を3週毎

に4サイクル行うものである。800例の登録を予定している。

2）骨盤放射線療法と化学療法＋腔内照射の比較をリンパ節転移陰性の子宮体癌に行う無作為化比較試験

3）手術進行期を決定してリンパ節転移があった症例に化学療法を追加する群と手術なしに骨盤照射と化学療法の併用を行う群の無作為化比較試験

B）さらに進行子宮体癌への治療としてⅢ期症例の術後地固め療法として，NSGO/EORTCの今回の発表の延長として全身化学療法に放射線療法の有無による無作為化比較試験も期待される。

C）そして最後に再発子宮体癌症例に対する治療としては，孤立性の骨盤内再発にはGOG238すなわち放射線療法単独かCDDP併用放射線療法の比較試験が現在進行中である。さらにⅣ期または再発子宮体癌の治療としてPTXはGOG209，TAP vs TCにおいて標準治療の一部として汎用されているし，欧州でのAPとCBDCA/Doxil（liposomal DXR）の比較試験も進行中である。さらには分子標的薬剤CC1-779に化学療法やホルモン療法を併用する臨床試験がGCIGを中心に展開されている。

以上が今後期待される臨床試験としてまとめられた。

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Feasibility Study of Docetaxel and Nedaplatin for Recurrent Squamous Cell Carcinoma of the Uterine Cervix

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Abstract. *Background: To determine a new taxane plus platinum treatment regimen for squamous cell carcinoma of the uterine cervix (CSCC), a phase I feasibility study of docetaxel (DTX) plus nedaplatin (CDGP) combination therapy was conducted. Patients and Methods: Twenty consecutive patients were enrolled into the study. The starting dose of DTX/CDGP was 60 mg/m^2 / 80 mg/m^2, every 4 weeks for at least three courses and the dose was escalated to 70 mg/m^2 / 100 mg/m^2. DTX 60 mg/m^2 / CDGP 100 mg/m^2 was also evaluated as an extra dose level. Results: Dose-limiting toxicity was granulocytopenia and the maximum tolerated dose was determined as 70 mg/m^2 / 100 mg/m^2. All 20 patients had measurable disease and a partial response was achieved in 8 (40.0%) patients. Conclusion: DTX/CDGP therapy appears to be a tolerable regimen for cervical squamous cell carcinoma, even in patients previously treated by cisplatin concurrent chemoradiotherapy. The recommended doses of DTX and CDGP were determined to be 60 mg/m^2 and 100 mg/m^2, respectively.*

Previous phase III studies of chemotherapy for recurrent or advanced squamous cell carcinoma of the uterine cervix (CSCC) (1-4) have revealed that cisplatin is the key chemotherapeutic drug; the addition of bleomycin did not improve patient survival and combined treatment with paclitaxel or topotecan plus cisplatin yielded superior survival to that with cisplatin alone. Combined paclitaxel and cisplatin (TP) therapy is thought to be an effective regimen, because the Gynecologic Oncology Group (GOG) 169 trial (3) reported an overall response rate of 46% even among patients with recurrent CSCC with a history of having undergone radiation therapy. However, TP therapy includes several problems such as the inconvenience of 24 hour administration of paclitaxel and the high incidence of neurotoxicity. Since *in vitro* (5) and *in vivo* (6) studies have reported the efficacy of *cis*-diammine (glycolato) platinum (CDGP; Nedaplatin), especially in cases of squamous cell carcinoma, the effects of CDGP-based combination chemotherapy have been studied in carcinoma of the uterine cervix (7), esophagus (8) and head and neck (9). Moreover, a recent phase I/II study of irinotecan plus CDGP therapy reported an overall response rate of 68%, including 2 complete responses in 27 patients with advanced or recurrent CSCC (7). Docetaxel (DTX) had a significantly lower neurotoxicity than and comparable activity with paclitaxel combined with carboplatin for ovarian cancer (10). In patients with advanced or recurrent CSCC, single agent docetaxel demonstrated tumor activity with a response rate of 13% (11). Therefore, to determine the feasibility of DTX/CDGP as an optional regimen for patients with CSCC, a phase I study was conducted in patients with recurrent CSCC.

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Key Words: Feasibility, cervical cancer, docetaxel, nedaplatin, chemotherapy.

Patients and Methods

The present study was conducted as a phase I dose escalation study. The protocol was approved by the Institutional Review Committee of Kinki University School of Medicine, and full informed consent was obtained from all the patients prior to their enrollment in the study. The eligibility criteria for inclusion in the study are shown in Table I. The criteria for starting the next treatment course are shown in Table II. DTX/CDGP treatment was planned for 4-weekly administration, beginning at an initial dose of DTX 60 mg/m^2 and CDGP 80 mg/m^2, with the dose escalated to 70 mg/m^2 / 80 mg/m^2, 70 mg/m^2 / 90 mg/m^2 and 70 mg/m^2 / 100 mg/m^2. However, since the highest dose level was considered to be the maximum tolerated dose (MTD) and at the second highest dose level disease progression was observed (see Results), an additional dose level (60 mg/m^2 / 100 mg/m^2) was evaluated. CDGP (Aqupla; Shionogi & Co. Ltd, Osaka, Japan) was administered intravenously over 90 minutes, followed by intravenous administration of DTX (Taxotere; Sanofi-Aventis K.K., Tokyo, Japan) over 90 minutes. Premedication prior to the administration of DTX consisted of the intravenous administration of dexamethasone (8 mg)

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Table I. *Eligibility criteria.*

1.	Recurrent uterine cervical squamous cell carcinoma
2.	Measurable region to determine direct effects of chemotherapy
3.	Performance status ≤ ECOG 2
4.	Normal ECG
5.	No active infectious diseases or active inflammatory diseases
6.	Leukocyte count ≥4,000/mm^3 and <12,000/mm^3
7.	Granulocyte count ≥2,000/mm^3
8.	Platelet count ≥100,000/mm^3
9.	Hemoglobin level ≥9.0 g/dl
10.	Serum total bilirubin ≤1.5 mg / dl
11.	Normal serum creatinine
12.	GOT, GPT within 2 x normal value
13.	Full informed consent from patient obtained

ECOG: Eastern Cooperative Oncology Group; ECG: electrocardiogram; GOT: glutamic-oxaloacetic transaminase; GPT: glutamic-pyrubic transaminase.

Table II. *Criteria for starting next treatment course.*

1.	Leukocyte count ≥3,000/mm^3 and <12,000/mm^3
2.	Granulocyte count ≥1,500/mm^3
3.	Hemoglobin level ≥8.0 g/dl
4.	Platelet count ≥50,000/mm^3
5.	Performance status ≤ECOG 2
6.	Normal ECG
7.	GOT, GPT within 2.5 x normal value
8.	Serum creatinine within normal limit
9.	Fever <38.0°C
10.	Non-hematological toxicity* CTCAE ≤ Grade 1
11.	No progressive disease

ECOG: Eastern Cooperative Oncology Group; ECG: electrocardiogram; GOT: glutamic-oxaloacetic transaminase; GPT: glutamic-pyrubic transaminase; CTCAE: Common Terminology Criteria for Adverse Events, 2003. *Not including nausea, vomiting, and alopecia.

and granisetron (3 mg) over 30 minutes and hydration with a total intravenous fluid volume of 2000 ml. Granulocyte-colony stimulating factor (G-CSF) support was only employed for those patients who exhibited Common Terminology Criteria for Adverse Events (CTCAE) grade 4 neutropenia or febrile neutropenia and none of the patients received prophylactic G-CSF supplementation. The dose-limiting toxicities (DLTs) were defined as grade 4 granulocytopenia lasting for over 5 days, grade 4 thrombocytopenia, febrile neutropenia (granulocytopenia ≤,1000/mm^3 and body temperature ≥38.5°C, grade 3/4 non-hematological toxicity excluding nausea, vomiting, and alopecia or treatment delay of more than 6 weeks due to toxicity. Toxicity was graded by the National Cancer Institute Common Toxicity Criteria, version 2.0. Three patients were entered at the initial dose level and monitored for DLT. If no DLT was observed, three additional patients were treated at the next higher dose level until DLT was observed or the maximum dose level was reached in the absence of DLT. If one of the three patients developed DLT at any level, the cohort was expanded to three additional patients, and if no DLT was observed in the three additional cases, the treatment dose was escalated to the next level. Maximum tolerated dose (MTD) was determined as the dose level at which no more than one out of six patients experienced a DLT. The direct antitumor effects were determined based on the criteria proposed in the new guidelines to evaluate the response to treatment in solid tumors (12).

Table III. *Characteristics of patients.*

Number of patients	20
Mean age (range)	52.4±8.0 years (28-66)
PS	
0	8
1	10
2	2
Prior treatment	
CCRT alone	7
RT alone	2
RH alone	2
RH + adjuvant CCRT	6
RH + adjuvant RT	3
Recurrent site	
Prior irradiation area	9
Extra irradiation area	7
Both	2
No prior irradiation	2
Median no. of treatment courses (range)	5.5 (1-11)

PS: Performance status determined by Eastern Cooperative Oncology Group Criteria; CCRT: cisplatin concurrent chemoradiotherapy; RT: radiation; RH: radical hysterectomy.

Results

Between August 2004 and November 2006, a total of 20 patients were enrolled into the study. The clinicopathological characteristics of the patients are listed in Table III. Table IV shows results of the present phase I dose escalation study. Among the patients receiving the DTX/CDGP therapy, 1 out of the 6 patients developed DLT (neutropenia) at level 3 (DTX 70 mg/m^2 / CDGP 90 mg/m^2), and 2 out of the 5 patients developed DLT (neutropenia with a delay of planned treatment by over 2 weeks and febrile neutropenia) at level 4 (DTX 70 mg/m^2 / CDGP 100 mg/m^2). Six out of the 17 patients (35.3%) given dose levels 1-4 showed a partial response. At dose levels 1 and 3, disease progression was observed. Three patients given the extra dose level (DTX 60 mg/m^2 / CDGP 100 mg/m^2) had no DLT. Two out of the 3 patients at this dose level showed a partial response. Disease progression was not observed at this dose level. Two patients had received no radiation therapy, four patients had disease within the irradiation field and two patients had disease outside the irradiation field among the patients who responded to DTX/CDGP.

Leukopenia (75.0%) and granulocytopenia (85.0%) were the most frequently observed CTCAE grade 3/4 hematological toxicities, and 12 patients (60.0%) needed G-CSF support. Other grade 3 toxicities observed were

Table IV. *Summary for each dose level.*

Dose level	DTX CDGP	Number of patients	Prior therapy	Total treatment courses	DLT	Best response
1	60 mg/m^2	3	CCRT	6		SD
	80 mg/m^2		CCRT	3		PD
			RT	7		SD
2	70 mg/m^2	3	RH+RT	6		SD
	80 mg/m^2		RH+RT	6		PR
			CCRT	6		SD
3	70 mg/m^2	6	CCRT	11		SD
	90 mg/m^2		CCRT	3		PR
			RH+CCRT	2	NEU	PD
			RH	8		PR
			RH	6		PR
			RH+CCRT	4		PD
4	70 mg/m^2	5	RH+RT	5		PR
	100 mg/m^2		CCRT	2	FN	SD
			RH+CCRT	4		SD
			RH+CCRT	3		PR
			CCRT	1	NEU	SD
EX	60 mg/m^2	3	RH+CCRT	7		PR
	100 mg/m^2		RT	11		PR
			RH+CCRT	3		SD

DTX: Docetaxel; CDGP: nedaplatin; CCRT: cisplatin concurrent chemoradiation; RT: radiation therapy; RH: radical hysterectomy; DLT: dose limiting toxicity; NEU: neutropenia; FN: febrile neutropenia; SD: stable disease; PR: partial response; PD: progressive disease; EX: extra dose level.

anemia (2 patients), thrombocytopenia (1 patient), nausea (5 patients), and vomiting (1 patient). Two patients exhibited a grade 1 allergic reaction soon after the start of DTX administration. None of the patients exhibited neurotoxicity. All of the patients with adverse effects, including those with DLTs, recovered within 3 weeks and no treatment-related deaths were observed.

Discussion

Dose level 4 (DTX 70 mg/m^2 / CDGP 100 mg/m^2) was determined as the MTD for DTX/CDGP, and three patients at level 1 and 3 had disease progression. In contrast, the three patients at the extra dose level (DTX 60 mg/m^2 / CDGP 100 mg/m^2) had no DLT and two of these patients responded to the DTX/CDGP. Therefore the recommended treatment dose for a subsequent phase II study was determined as the extra dose level, DTX 60 mg/m^2 / CDGP 100 mg/m^2, administered every 4 weeks. While the effects of platinum-based combination chemotherapy alone for recurrent CSCC have been unsatisfactory, survival benefit of CCRT both as a primary therapy (13-16) and an adjuvant therapy (17) has been shown in patients with CSCC. CCRT has been widely used as the standard treatment for patients with CSCC. However, the treatment options for recurrent CSCC after CCRT are limited because the overall response rate to platinum-based chemotherapy in cases of recurrent CSCC has been reported to be around 20% (18) in chemotherapy-naive patients, and 5.3% (19) in patients with recurrent disease within the previously irradiated field. Therefore, the establishment of an effective chemotherapeutic regimen for CCRT-treated patients with recurrent CSCC is urgently needed to improve the long-term prognosis of such patients. Based on the results of our present study, CDGP-based chemotherapy may be effective even for cases with disease within the previous irradiation field, although the treatment results remain unsatisfactory.

The efficacy (9-13% for overall response) of DTX alone was limited for patients with advanced or recurrent CSCC who had received previous chemotherapy (11, 20). Subsequent studies should be planned carefully to observe the efficacy of DTX/CGDP. Large-scale phase II studies of DTX/CDGP and the combination of CDGP and paclitaxel as another taxane for a calibration may be needed to discover a therapy improving the long-term prognosis of patients with recurrent CSCC previously treated by CCRT or radiation therapy.

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