[考　察]

今回の検討では子宮体癌の再発症例中12.7%(8/63)が、治療開始後5年以降に再発していた。悪性腫瘍は一般に治療開始後5年間再発なければ治癒した可能性が高いと考えられており、「5年生存率」が治療成績に用いられる程、5年という期間は重要である。しかし乳癌は再発症例の25%以上が治療開始後5年以降に再発し、これは特にホルモン療法を施行した症例に多いとされるなど[14]、5年に拘らない考えが出てきている。今回の検討で、経過観察5年以降に再発した症例の50%が高分化型類内膜腺癌であったことからも、子宮体癌は治療開始後5年以降でも再発する症例があり、十分な経過観察が必要であると考えられる。

子宮体癌の経過観察に関する研究は、表1に示す様にいくつか報告されているが、必ずしも十分な症例数がある訳ではなく、また長期にわたる経過観察期間で検討している訳ではない[1)-13)]。悪性腫瘍の経過観察は長期間を要するため、前向きな研究が計画しにくく、適確な情報が得にくい。また施行された治療により、再発までの期間や再発部位が変わる可能性があることから、標準治療が変わる度に再検討を要することになる。このように経過観察に関する研究には根本的な問題点が多く、解析が難しいが、主に検討すべき点は経過観察の間隔と来院時に行う検査である。残念ながら今回は検討されておらず、今後の重要な検討課題である。

今回の検討で、治療開始後1年以内で再発した症例が41.3%(26/63)、1～2年で再発した症例が27.0%(17/63)と多いことから、この期間は厳重な経過観察が必要なのかもしれない。しかし1年以内に再発した症例の再発後生存期間の中央値は4.0ヶ月であり、再発を早期に診断することは治療成績の改善や延命に貢献しない様である。逆に初回治療後1年以降に再発した症例は1年程度かそれ以上の生存が期待できることから、再発後の生活の質(QOL)維持が良いほうが望ましく、再発の早期診断のために厳重な経過観察する必要があることになる。しかしこの時期以降は再発の危険性が少なくなっていくため、全ての症例の経過観察を厳重にすべきではなく、今後の重要な検討課題である。

経過観察の間隔と同様に、経過観察時に行うべき検査も重要な論点である。今回の検討では子宮体癌での頻度の高い再発部位は、肺(28.6%)・骨盤内(27.0%)・腹腔内(22.0%)・傍大動脈リンパ節(17.5%)であり、これらを精査するには定期的にCT等の画像診断を行うのが望ましいことになる。しかし経過観察に関する文献をみると、CTを毎年施行しているのは12文献中わずか1つで、腫瘍マーカーCA125を測定している文献はない。また疼痛などの臨床症状により再発が診断される可能性が77%と報告されていること、CTは被爆量が多いことから頻回に行いにくく、これも今後の重要な検討課題である。

緒言にも書いたが悪性腫瘍の経過観察に関する報告は、診断や治療に関する文献に比べて非常に少ない。筆者が10年以上前に検索した時点では参考文献は得られず、欧米の教科書に「6ヶ月毎に全ての検査を行う」と書いてあるのみで、慣習的に上司や先輩の真似をして1年目は1ケ月ごと、2年目は2ケ月ごと、3年目は3ケ月ごと、4～5年目は6ケ月ごと、6年目以降は1年ごと、みたいな間隔で経過観察を行っていた。しかし以後の検討により現在は諸般の事情等も加味して、1～2年目は3ケ月ごと、3年目以降は6ケ月ごとに経過観察している。来院時に行う検査などさらに検討すべき事項が残されており、子宮体癌の経過観察は今後も重要な課題であると考えられた。

[参考文献]

1. Fung-Kee-Fung M, Dodge J, Elit L, *et al*. Follow-up after primary therapy for endometrial cancer: A systematic review. *Gynecol Oncol* 2006; **101**: 520-529
2. Morice P, Levy-Piedbois C, Ajaj S, *et al*. Value and cost evaluation of routine follow-up for patients with clinical stage I/II endometrial cancer. *Eur J Cancer* 2001; **37**: 985-990
3. Owen P, Duncan ID. Is there any value in the long term follow up of women treated for endo-

metrial cancer? *Br J Obstet Gynaecol* 1996; **103**: 710-713

4. Gadducci A, Cosio S, Fanucchi A, *et al.* An intensive follow-up does not change survival of patients with clinical stage I endometrial cancer. *Anticancer Res* 2000; **20**: 1977-1984
5. Agboola OO, Grunfeld E, Coyle D, *et al.* Costs and benefits ofroutine follow-up after curative treatment for endometrial cancer. *CMAJ* 1997; **157**: 879-886
6. Gordon AF, Owen P, Chien PFW, *et al.* A critical evaluation of follow-up of women treated for endometrial adenocarcinoma. *J Obstet Gynaecol* 1997; **17**: 386-389
7. Ng TY, Ngan HYS, Cheng DKL, *et al.* Vaginal vault cytology in the routine follow-up of patients treated for endometrial carcinoma: is it useful? *Aust NZ J Obstet Gynaecol* 1997; **37**: 104-106
8. Salvesen HB, Akslen LA, Iversen T, *et al.* Recurrence of endometrial carcinoma and the value of routine follow up. *Br J Obstet Gynaecol* 1997; **104**: 1302-1307
9. Berchuck A, Anspach C, Evans AC, *et al.* Post-surgical surveillance of patients with FIGO stage I/II endometrial adenocarcinoma. *Gynecol Oncol* 1995; **59**: 20-24
10. Reddoch JM, Burke TW, Morris M, *et al.* Surveillance for recurrent endometrial carcinoma: development of a follow-up scheme. *Gynecol Oncol* 1995; **59**: 221-225
11. Shumsky AG, Stuart GC, Brasher PM, *et al.* An evaluation of routine follow-up of patients treated for endometrial carcinoma. *Gynecol Oncol* 1994; **55**: 229-233
12. Podczaski E, Kaminski P, Gurski K, *et al.* Detection and patterns of treatment failure in 300 consecutive cases of "early" endometrial cancer after primary surgery. *Gynecol Oncol* 1992; **47**: 323-327
13. MacDonald JH, Kidd GM. An audit of endometrial carcinoma: the value of routine follow up. *J Obstet Gynaecol* 1990; **10**: 548-550
14. Hayes DF. Clinical practice. Follow-up of patients with early breast cancer. *N Engl J Med* 2007; **356**(24): 2505-2513

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Phase II Clinical Trial of Pegylated Liposomal Doxorubicin (JNS002) in Japanese Patients with Müllerian Carcinoma (Epithelial Ovarian Carcinoma, Primary Carcinoma of Fallopian Tube, Peritoneal Carcinoma) Having a Therapeutic History of Platinum-based Chemotherapy: A Phase II Study of the Japanese Gynecologic Oncology Group

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Objective: This study was conducted to evaluate the efficacy and safety of pegylated liposomal doxorubicin (PLD) in Japanese patients with Müllerian carcinoma having a therapeutic history of platinum-based chemotherapy.

Methods: Patients who were diagnosed with Müllerian carcinoma (epithelial ovarian carcinoma, primary carcinoma of fallopian tube and peritoneal carcinoma) by histological examination and had received the initial platinum-based chemotherapy were included in the study. The study drug was administered to the patients at 50 mg/m^2 every 4 weeks.

Results: Seventy-four patients were enrolled in the study. All patients had received platinum-based chemotherapy as first-line regimen and more than 90% of patients had also received taxanes. The overall response rate was 21.9% (95% confidence interval, 13.1–33.1%) and 38.4% of patients had stable disease. The median time to progression was 166 days. The major non-haematological toxicities were hand-foot syndrome (Grade 3; 16.2%) and stomatitis (Grade 3; 8.1%). Myelosuppression such as leukopenia (Grade 3; 52.7%, Grade 4; 6.8%), neutropenia (Grade 3; 31.1%, Grade 4; 36.5%) and decreased haemoglobin (Grade 3; 14.9%, Grade 4; 2.7%) were the most common haematological toxicities.

Conclusion: We confirmed that a 50 mg/m^2 every 4 weeks regimen of PLD was active in Japanese patients with Müllerian carcinoma having a therapeutic history of platinum-based chemotherapy and toxicity was manageable by dose modification of PLD or supportive care.

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Key words: pegylated liposomal doxorubicin – Müllerian carcinoma – ovarian carcinoma – hand-foot syndrome – chemo-gynaecology – chemo-phase I-II-III – gynaecology

INTRODUCTION

Approximately 8000 cases of ovarian cancer are newly diagnosed in Japan and more than 4000 women die of this disease (1). From an embryologic perspective, epithelial ovarian carcinoma, primary carcinoma of fallopian tube and peritoneal carcinoma are generally recognized as a similar disease group, which is known as Müllerian carcinoma. In patients with primary carcinoma of the fallopian tube and peritoneal carcinoma, the experience with chemotherapeutic agents is largely limited to case reports and small studies due to the rarity of disease type (2,3). However, the overall experience closely parallels that of ovarian cancer, so treatment of primary carcinoma of the fallopian tube and peritoneal carcinoma is conducted according to that of ovarian cancer (2,3).

Advanced epithelial ovarian cancer is a highly chemosensitive solid tumour with response rates to first-line chemotherapy of ~80%. The majority of patients, however, eventually relapse and treatment with second-line agents becomes necessary. Furthermore, patients with recurrent ovarian cancer ultimately die of chemoresistant disease. Therefore, it is very important to recognize recurrent ovarian cancer therapy as palliative therapy and therapeutic agents are required to show efficacy as well as favourable toxicity profile. However, there are not many drugs approved in Japan for ovarian carcinoma, or recommended by the Japanese clinical practice guideline for as second-line treatment except platinum, taxane and irinotecan.

Pegylated liposomal doxorubicin (PLD) is a formulation of doxorubicin hydrochloride encapsulated in long circulating STEALTH® liposomes and formulated for intravenous administration. STEALTH® liposomes have liquid membranes coated with polyethylene glycol, which attracts water and renders resistance to mononuclear phagocytosis (4). The liposome's small diameter (~100 nm) and their persistence in the circulation allow their penetration into altered and often compromised, leaky tumour vasculature with entry into the interstitial space in malignant tissues (5). Therefore, pegylated liposomes are suitable for prolonged delivery of doxorubicin and have a prolonged circulation time (6,7). At these tumour sites, the accumulating liposomes gradually break down, releasing doxorubicin to the surrounding tumour cells (8,9). PLD has been designed to enhance the efficacy and to reduce the toxicities of doxorubicin such as myelosuppression, alopecia and cardiotoxicity by altering the plasma pharmacokinetics and tissue distribution of the drug.

Based on the data from the Phases II and III clinical trials in Europe and the USA, it is evident that PLD possesses promising activity and a favourable toxicity profile in the second-line treatment of ovarian cancer (10–15). Currently, PLD is provided as one of the standard treatment options in recurrent ovarian cancer treatment guidelines (16–18).

The result of the Phase I clinical trial in Japan was reported (19). In that study, recommended PLD dose was evaluated in 15 Japanese patients with solid tumours and resulted in 50 mg/m^2 every 4 weeks. In addition, one partial response (PR) and one normalization of CA125 were observed among six ovarian cancer patients enrolled in that study, and further trials with Japanese ovarian cancer patients were encouraged.

Based on the result from a Phase I clinical trial in Japan, we conducted the Phase II clinical trial of PLD in patients with recurrent or relapsed Müllerian carcinoma (epithelial ovarian carcinoma, primary carcinoma of fallopian tube, peritoneal carcinoma) having a therapeutic history of platinum-based chemotherapy.

We conducted a multicentre, non-randomized, open-label study to evaluate efficacy and safety of a PLD 50 mg/m^2 every 4-week regimen in Japanese patients with Müllerian carcinoma who had previously been treated with platinum-based chemotherapy.

PATIENT AND METHODS

Study Design

This study was a multicentre non-randomized, open-label trial to evaluate efficacy and safety of PLD in Japanese patients with Müllerian carcinoma previously treated with platinum-based chemotherapy. The primary endpoint was the best overall response (response rate) and secondary endpoints included adverse events and adverse drug reactions (incidence, severity, seriousness and causality), time to response and duration of response. The final evaluation of the antitumour effect was performed by the independent radiological review committee. The study protocol was approved by the institutional review board at each site. This study was conducted based on ethical principles in the Declaration of Helsinki and in compliance with Good Clinical Practice.

Patients

This study included patients who met all the following inclusion criteria: (i) having histological confirmation of Müllerian carcinoma (epithelial ovarian carcinoma, primary fallopian tube carcinoma and peritoneal carcinoma);

(ii) receiving first-line platinum-based chemotherapy and who would receive PLD as a second-line therapy if time to progression was within 12 months from the date of final administration of platinum therapy, excluding patients whose best response to first-line platinum-based chemotherapy was progressive disease (PD), or who received PLD as a third-line therapy; (iii) receiving 1 or 2 regimens with prior chemotherapy; (iv) having measurable lesions that conformed to the Response Evaluation Criteria in Solid Tumours (RECIST) criteria; (v) ECOG performance status (PS) grade of 0–2; (vi) adequate functions of principal organs, defined by white blood cell (WBC) counts 3.0×10^3–$12.0 \times 10^3/mm^3$, neutrophil counts not less than $1.5 \times 10^3/mm^3$, haemoglobin not less than 9.0 g/dl, platelet count not less than $10.0 \times 10^4/mm^3$, serum AST, ALT and AP not more than 2.5 times the institutional upper limit of normal, total bilirubin not more than the institutional upper limit of normal, serum creatinine not more than 1.5 times the institutional upper limit of normal, left ventricular ejection fraction (LVEF) not less than 50%, electrocardiography (ECG) normal or minor change without symptoms that required any therapeutic intervention, and no evidence of cardiac disorder or Class I in New York Heart Association (NYHA) functional classification; (vii) no colony stimulating factor (CSF) agent or blood transfusion received within 2 weeks before the date of blood tests for screening; (viii) no previous treatment with hormonal agents, oral antimetabolic or immunotherapeutic agents for at least 2 weeks, with nitrosourea or mitomycin C at least 6 weeks, or with surgical therapy, radiation therapy or other chemotherapy for 4 weeks or more; (ix) abilities to stay in hospital for 4 consecutive weeks from the initial administration of PLD; (x) survival expectancy 3 months or longer; (xi) 20–79 of age years at enrolment in the trial; and (xii) received an explanation of this trial from the physicians with written informed consent forms and other relevant information and freely provided informed consent before the trial.

Patients who met any of the following exclusion criteria were excluded from the trial: (i) requiring drainage of pericardial fluid; (ii) having experienced myocardial infarction or angina attack within 90 days before the start of trial; (iii) receiving prior therapy with anthracycline (total anthracycline dose of more than 250 mg/m^2 as doxorubicin); and (iv) having known hypersensitivity to doxorubicin or any component of PLD.

Medication

PLD was intravenously administered to each subject at a dose of 50 mg/m^2 as doxorubicin hydrochloride on Day 1 of each cycle, followed by a treatment-free interval of 28 days including Day 1. This was repeated for at least two cycles if the subject did not meet the withdrawal criteria. PLD was administered at a rate of 1.0 mg/min from the start of infusion to completion, using an infusion pump in consideration of risks of development of infusion-related reactions. PLD was used by diluting with 250 ml of 5% glucose injection for a dose of less than 90 mg as doxorubicin hydrochloride or with 500 ml for a dose of 90 mg or more as doxorubicin hydrochloride.

After administration, PLD would be discontinued in subjects who met any of the following withdrawal criteria: (i) desiring to discontinue the study treatment or withdrawing consent; (ii) having LVEF decreased to less than 45% after administration of PLD or decreased by 20% or more than baseline; (iii) having no possibility for a subsequent cycle to be started within 6 weeks from the planned injection date because of adverse reactions or after 8 weeks for hand-foot syndrome (HFS) or stomatitis; (iv) having bilirubin increased to 3.0 mg/dl or more; (v) requiring a repeated reduction in the dose; (vi) the anticipated total dose of anthracycline antibiotics including PLD would exceed 500 mg/m^2 as doxorubicin hydrochloride (including doses from prior chemotherapy and pre/postoperative treatment); (vii) being judged by the physician to have difficulties continuing the trial due to serious (or significant) adverse events; (viii) being assessed to have difficulty continuing the trial due to concurrent illnesses (e.g. complications); (ix) having obvious progression of the underlying disease or development of new lesions (PD); (x) having any of the exclusion criteria which was discovered after enrolment; and (xi) being judged as unfavourable to continue the trial by the physician.

Prior to administration of the study drug in the next cycle, all the subjects were confirmed to meet all the following criteria: (i) HFS or stomatitis $\leq$Grade 1; (ii) neutrophil counts $\geq 1.5 \times 10^3/mm^3$; (iii) WBC counts $\geq 3.0 \times 10^3/mm^3$; (iv) platelet counts $\geq 7.5 \times 10^4/mm^3$; (v) bilirubin $\leq$1.5 mg/dl; and (vi) other adverse drug reactions $\leq$ Grade 2 (excluding fatigue, nausea, vomiting, anorexia, hypokalemia, hyponatremia and lymphopenia). If any of these criteria was not met, the scheduled administration of the study drug for the next cycle would be delayed for 2 weeks at the maximum. If any of the above criteria was still not met after a 2-week delay from the scheduled initial date of each cycle, the trial for the subjects would be discontinued. In case Grade 2 HFS or stomatitis was observed at 6 weeks from the initial date of each cycle, the scheduled administration of the test drug for the next cycle would be delayed for 2 weeks. As a result, when the subjects met all the above criteria, the next cycle would be started. Even if the subjects met all the criteria, the scheduled initial date could be delayed for a maximum of 2 weeks at the investigator's discretion.

As the subjects met any of the following dose reduction criteria, the previous dose would be reduced by 25% (37.5 mg/m^2) for the next cycle: (i) HFS or stomatitis $\geq$ Grade 3; (ii) neutrophil count $<500/mm^3$ or WBC count $<1000/mm^3$ that was maintained for at least 7 days; (iii) neutrophil counts $<1000/mm^3$ with 38.0°C or higher fever; (iv) platelet reduction $<2.5 \times 10^4/mm^3$; (v) other adverse drug reactions $\geq$ Grade 3 (excluding fatigue, nausea, vomiting, anorexia, hypokalemia, hyponatremia, lymphopenia and other adverse events associated with infusion-related reactions); and (vi) the physician judged that the dose should be

decreased. Dose reduction was permitted only once, and it was prohibited to increase the dose after the dose was reduced. If a further dose reduction was required after the dose was reduced, the trial for the subject would be discontinued.

Administration of CSF was admitted when patients met any of the following criteria: (i) neutrophil counts $<1000/mm^3$ with fever ($\geq 38°C$); (ii) neutrophil counts $<500/mm^3$; (iii) experience of either (i) or (ii) in the prior cycle and neutrophil counts $<1000/mm^3$ in the following cycle.

Evaluation of Response and Safety

Tumour response evaluation was performed according to the RECIST guidelines. Confirmed duration of stable disease (SD) was defined as the duration of 8 consecutive weeks or longer after the start of administration.

Severity of adverse events was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.

Sample Size and Statistical Analysis

Among the subjects enrolled in this trial, those who received platinum-based chemotherapy as the first-line chemotherapy and experienced disease progression between 6 and 12 months after the completion of the platinum regimen were classified as the platinum-sensitive group, and those who had progression during the first-line chemotherapy, received platinum-based chemotherapy as the first-line chemotherapy and experienced progression less than 6 months after the completion of the platinum regimen, or who would receive PLD as a third-line therapy were classified as the platinum-resistant group. A sample size to produce the expected response rate of 30 and 15% for the platinum-sensitive and platinum-resistant groups, respectively, with the threshold response rate of 5%, a significance level of 5% and power of 80% was determined to be 80 patients in total (20 and 60 patients for the platinum-sensitive and platinum-resistant groups, respectively).

For the response evaluation, statistical analysis was performed based on the evaluation for the full analysis set (FAS) by the independent radiological review committee. The primary endpoint was the response rate, the proportion of patients with complete response (CR) or PR in the response analysis set, and the point estimate and two-sided 95% confidence interval (CI) were calculated. The secondary endpoints included the duration of overall response, time to response and time to progression, and the progression-free survival was analysed using the Kaplan–Meier method, and descriptive statistics (median, minimum and maximum) were calculated. The safety of PLD was evaluated for all the subjects treated with PLD. Statistical analyses were performed using the SAS System for Windows release 8.02.

RESULT

Demographics and baseline characteristics of patients are shown in Table 1. Seventy-four patients were enrolled into the trial between January and December 2005, and 73 patients (11 for the platinum-sensitive group and 62 for the platinum-resistant group), excluding one patient who was confirmed to be ineligible after enrolment, were eligible for the trial, and defined as the FAS. All 74 patients who received PLD were defined as the safety analysis set. Although the targeted number of patients for the platinum-sensitive group was 20, only 11 patients were enrolled. That was because the study was closed at the end of 2005 when the patient enrolment in the platinum-resistant group reached the target number due to slow enrolment.

The median of patients' age was 57.0 years (range, 32–76). Among 74 patients enrolled, 62 had epithelial ovarian carcinoma and 12 had peritoneal carcinoma. Histological, 49 patients had serous carcinoma, eight had endometrioid carcinoma, eight had clear cell carcinoma, one had mucinous carcinoma and eight had other types of carcinoma. All 74 patients had received first-line chemotherapy including platinum regimen, 70 (94.6%) had also received taxanes as the first-line chemotherapy, and only three had received anthracycline in the prior chemotherapy. A total of 334 cycles of PLD was administered to 74 patients, and the median number of cycles administered was 4.0 (range, 1–10 cycles). Administration of PLD was completed or discontinued in all 74 patients before statistical analysis. The dose of PLD was reduced to 37.5 mg/m^2 in 26 of 74 patients (35.1%). The scheduled administration of PLD was delayed in 49 of 74 patients (66.2%) and in 154 of 334 cycles (46.1%).

Response

The antitumour effect (best overall response) and response rate are shown in Table 2. The best overall response in 73 patients of FAS was CR in two patients, PR in 14, SD in 28, PD in 27 and not evaluable (NE) in two patients. The response rate was 21.9% (16 of 73) (95% CI: 13.1–33.1%). The response rate (two-sided 95% CI) by patient group was 27.3% (3 of 11) (95% CI: 6.0–61.0%) in the platinum-sensitive group and 21.0% (13 of 62) (95% CI: 11.7–33.2%) in the platinum-resistant group. The proportion of patients with CR, PR or SD was 60.3% (44 of 73) in FAS, and 54.5% (6 of 11) in the platinum-sensitive group and 61.3% (38 of 62) in the platinum-resistant group.

The results from subgroup analysis sets by platinum-free interval were as follows. In a subgroup analysis set where patients received PLD as a second-line therapy, the response rate by platinum-free intervals was 8.3% (1 of 12) and 27.3% (3 of 11) in patients with the platinum-free interval of within 6 months and of 6–12 months, respectively. In another subgroup analysis set where patients received PLD as a third-line therapy, the response rate was 7.1% (1 of 14),

Table 1. Demographics and baseline characteristics of patients

Characteristics	Total ($n = 74$)	Platinum sensitive ($n = 11$)	Platinum resistant ($n = 63$)
Age, years			
Median (range)	57.0 (32–76)	55.0 (40–72)	58.0 (32–76)
Primary cancer (%)			
Epithelial ovarian carcinoma	62 (83.8)	11 (100.0)	51 (81.0)
Peritoneal carcinoma	12 (16.2)	0 (0.0)	12 (19.0)
Tumour histology (%)			
Serous	49 (66.2)	6 (54.5)	43 (68.3)
Endometrioid	8 (10.8)	3 (27.3)	5 (7.9)
Clear cell	8 (10.8)	1 (9.1)	7 (11.1)
Mucinous	1 (1.4)	0 (0.0)	1 (1.6)
Other	8 (10.8)	1 (9.1)	7 (11.1)
Initial FIGO stage (%)			
I	7 (9.5)	1 (9.1)	6 (9.5)
II	1 (1.4)	1 (9.1)	0 (0.0)
III	50 (67.6)	6 (54.5)	44 (69.8)
IV	16 (21.6)	3 (27.3)	13 (20.6)
Previous chemotherapy (%)			
1 regimen	23 (31.1)	11 (100.0)	12 (19.0)
2 regimen	50 (67.6)	0 (0.0)	50 (79.4)
3 regimen	1 (1.4)	0 (0.0)	1 (1.6)
Previous chemotherapy with antracycline (%)			
Yes	3 (4.1)	0 (0.0)	3 (4.8)
No	71 (95.9)	11 (100.0)	60 (95.2)
Platinum-free interval (days)			
Median (range)	263 (28–2792)	315 (216–441)	235 (28–2792)
CA-125 at baseline (U/ml)			
Median (range)	243.6 (5.8–7809.8)	192.1 (22.2–808.0)	261.0 (5.8–7809.8)

FIGO, Federation Internationale de Gynecologie et d'Obstetrique.

Table 2. Response rate

	Total	Platinum sensitive	Platinum resistant
Number of patients	73	11	62
Best overall response: *n* (%)			
CR	2 (2.7)	0 (0.0)	2 (3.2)
PR	14 (19.2)	3 (27.3)	11 (17.7)
SD	28 (38.4)	3 (27.3)	25 (40.3)
PD	27 (37.0)	4 (36.4)	23 (37.1)
NE	2 (2.7)	1 (9.1)	1 (1.6)
Response rate			
n (%) (95% CI)	16 (21.9) (13.1–33.1)	3 (27.3) (6.0–61.0)	13 (21.0) (11.7–33.2)

CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; NE, not evaluable; 95% CI, confidence interval.

15.4% (2 of 13) and 36.8% (7 of 19) in patients with the platinum-free interval of within 6 months, of 6–12 months and more than 12 months, respectively.

The response rate by histological type was 29.2% (14 of 48) and 25.0% (2 of 8) in patients with serous carcinoma and with endometrioid carcinoma, respectively. In patients

Table 3. Time to response, duration of response and time to progression

	Total	Platinum sensitive	Platinum resistant
Number of patients	73	11	62
Time to response (day)			
Patient (%)[a]	16 (21.9)	3 (27.3)	13 (21.0)
Median (range)	54.0 (20–162)	56.0 (54–59)	52.0 (20–162)
Duration of response (day)			
Patient (%)[a]	16 (21.9)	3 (27.3)	13 (21.0)
Median (range)	149.0 (56–309)	– (92–159)	149.0 (56–309)
Withdrawal (%)	11 (68.8)	2 (66.7)	9 (69.2)
Time to progression (day)			
Patient (%)[b]	71 (97.3)	10 (90.9)	61 (98.4)
Median (range)	166.0 (14–358)	159.0 (16–217)	168.0 (14–358)
Withdrawal (%)	30 (42.3)	4 (40.0)	26 (42.6)

[a]Responder only. [b]Excluded two patients due to unable calculation for time to progression.

with clear cell carcinoma, SD was observed in two of eight patients, and the time to progression in the two patients was 350+ and 87+ days, respectively. In patients with mucinous carcinoma, SD was observed in one of one patient and the time to progression was 135+ days.

The median and range of the duration of response, time to response and time to progression are shown in Table 3.

The median time to response (CR or PR) was 54.0 days. The median time to response was 56.0 days in the platinum-sensitive group and 52.0 days in the platinum-resistant group.

The median duration of overall response was 149.0 days. The median duration of overall response in the platinum-resistant group was 149.0 days, however, that in the platinum-sensitive group could not be calculated. The Kaplan–Meier curve for time to progression is shown in Fig. 1. The median time to progression was 166.0 days: 159.0 days in the platinum-sensitive group and 168.0 days in the platinum-resistant group. The median survival could not be calculated.

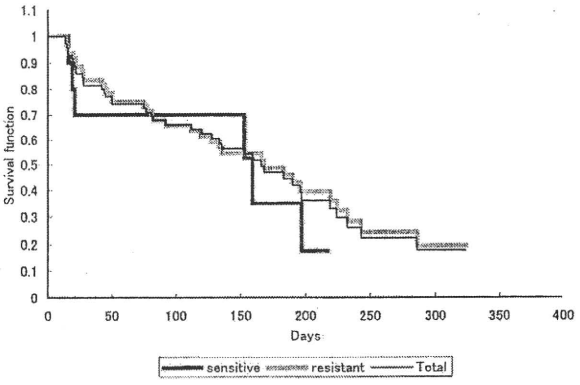

Figure 1. Kaplan–Meier estimates of time to progression.

Safety

Adverse drug reactions were reported from all 74 patients treated with PLD. The major adverse drug reactions observed in the study are shown in Table 4.

The most common Grade 3 or 4 adverse reactions were due to haematological toxicity: neutropenia in 50 patients (67.6%), leukopenia in 44 (52.7%), lymphopenia in 35 (47.3%), decreased haemoglobin in 13 (17.6%), thrombocytopenia in five (6.8%) and erythropenia in three patients (4.1%). The median time to nadir for neutrophils, WBCs, haemoglobin and platelets from the start of administration in the first cycle was 21.0 days, 21.0, 15.0 and 22.0 days, respectively. The median time to recovery to the level at which the administration of PLD in the next cycle was permitted was 7.0–8.0 days for any haematological event.

Grade 3 or 4 adverse drug reactions due to non-haematological toxicity included: HFS in 12 patients (16.2%), stomatitis in six (8.1%), febrile neutropenia, nausea, ALT (GPT) increased and blood potassium decreased in two each (2.7%) and deep venous thrombosis rash, herpes zoster, infection, upper respiratory tract infection, impaired glucose tolerance, diarrhoea, small intestinal obstruction, vomiting, fatigue, AST (GOT) increased, decreased blood sodium and increased γ-GTP in one each (1.4%). Only deep venous thrombosis was Grade 4. The median time to occurrence of HFS, rash and stomatitis from the start of administration was 34.0 days (2.0 cycles), 33.0 days (2.0 cycles) and 16.0 days (1.0 cycle), respectively. The median time to the Grade 2, 3 or 4 adverse reactions (Grade 3 or 4 for rash), which required delay of next administration, was 64.5 (3.0 cycles), 84.0 (3.0 cycles) and 43.0 (2.0 cycles), respectively and the median duration for those reactions was 15.0, 8.0 and 8.0 days, respectively.

Infusion-related reactions were seen in 14 patients (18.9%) only during the first cycle. Serious reactions were not seen.

Table 4. Grades 3 and 4 adverse drug reactions

Adverse Reaction (MedDRA/J Ver9.0)	Number of patients ($n = 74$)			
	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Neutropenia	8 (10.8)	11 (14.9)	23 (31.1)	27 (36.5)
Lymphocytopenia	15 (20.3)	16 (21.6)	29 (39.2)	6 (8.1)
Leukopenia	5 (6.8)	20 (27.0)	39 (52.7)	5 (6.8)
Haemoglobin decreased	23 (31.1)	27 (36.5)	11 (14.9)	2 (2.7)
Thrombocytopenia	27 (36.5)	13 (17.6)	4 (5.4)	1 (1.4)
Deep vein thrombosis	0 (0)	0 (0)	0 (0)	1 (1.4)
Hand-foot syndrome	20 (27.0)	26 (35.1)	12 (16.2)	0 (0)
Stomatitis	29 (39.2)	22 (29.7)	6 (8.1)	0 (0)
Erythropenia	42 (56.8)	11 (14.9)	3 (4.1)	0 (0)
Nausea	37 (50.0)	6 (8.1)	2 (2.7)	0 (0)
ALT (GPT) increased	16 (21.6)	1 (1.4)	2 (2.7)	0 (0)
Blood potassium decreased	10 (13.5)	0 (0)	2 (2.7)	0 (0)
Febrile neutropenia	0 (0)	0 (0)	2 (2.7)	0 (0)
Rash	17 (23.0)	19 (25.7)	1 (1.4)	0 (0)
Fatigue	28 (37.8)	5 (6.8)	1 (1.4)	0 (0)
Vomiting	11 (14.9)	5 (6.8)	1 (1.4)	0 (0)
γ-GTP increased	13 (17.6)	4 (5.4)	1 (1.4)	0 (0)
Diarrhoea	12 (16.2)	4 (5.4)	1 (1.4)	0 (0)
AST (GOT) increased	18 (24.3)	2 (2.7)	1 (1.4)	0 (0)
Upper respiratory tract infection	0 (0)	2 (2.7)	1 (1.4)	0 (0)
Blood sodium decreased	15 (20.3)	0 (0)	1 (1.4)	0 (0)
Small intestinal obstruction	0 (0)	0 (0)	1 (1.4)	0 (0)
Herpes zoster	0 (0)	0 (0)	1 (1.4)	0 (0)
Infection	0 (0)	0 (0)	1 (1.4)	0 (0)
Glucose tolerance impaired	0 (0)	0 (0)	1 (1.4)	0 (0)

Of these patients, one patient had Grade 2 events and other patients had Grade 1 events. Symptoms associated with infusion-related reactions included hot flushes, facial flushing and hot feeling. These symptoms were restored on the day of occurrence or the following day. PLD was discontinued in one patient who had nausea, low back pain, chest tightness and facial flushing as Grade 2 infusion-related reactions. These symptoms were rapidly restored by supportive care with drip infusion of physiological saline. Although slow-down in the PLD infusion rate was required in two patients, the other 11 patients completed the infusion without any intervention. Among 14 patients with infusion-related reactions, 11 patients received the next cycle without recurrence of infusion-related reactions.

Cardiac toxicity was seen in 17 of 74 patients (23.0%), all of which were Grade 1. Increase in the incidence of cardiac toxicity associated with accumulation of PLD was not observed. Alopecia was seen in 18 patients (24.3%), which was Grade 1 in all of them.

There was no death due to adverse events reported during the trial period. Fourteen serious adverse reactions were seen in 11 patients (14.9%): two events each of nausea, HFS, small intestinal obstruction and stomatitis; and one event each of neutropenia, leukopenia, vomiting, pneumonitis, deep venous thrombosis and anorexia.

PLD was discontinued due to adverse reactions in 16 (21.6%). Common adverse reactions that required the discontinuation of PLD included: decreased haemoglobin in six patients (8.1%), leukopenia in four (5.4%) and HFS and neutropenia in three each (4.1%). The PLD dose was reduced in 24 patients (32.4%) due to adverse drug reactions such as HFS in 10 patients (13.5%), decreased haemoglobin and stomatitis in five each (6.8%) and neutropenia in three patients (4.1%). Administration of PLD was delayed in 49 patients (66.2%) in 111 cycles of 334 cycles due to adverse reactions mainly including leukopenia in 68 cycles (20.4%), neutropenia in 56 cycles (16.8%), HFS in 40 cycles (12.0%) and stomatitis in eight cycles (2.4%).

DISCUSSION

We evaluated the efficacy and safety of PLD in Japanese patients with Müllerian carcinoma (epithelial ovarian carcinoma, primary fallopian tube carcinoma and peritoneal carcinoma) previously treated with platinum-based chemotherapy.

Currently, platinum and taxane therapies are used for the standard first-line chemotherapy for treatment of ovarian carcinoma, though the results of Phase III clinical trials conducted in the US and Europe demonstrated the effectiveness of PLD, gemcitabine and topotecan in patients resistant to these drugs (13,14,20). However, these drugs have not been approved and the results from prospective studies of their use in patients with ovarian carcinoma previously treated with platinum and taxane therapy have not been reported in Japan. Our study was intended to provide the outcome in patients who had recurrent Müllerian carcinoma after the standard first-line chemotherapy (90% of patients in our study had received first-line chemotherapy with platinum and taxane).

In this trial, the response rate was 21.9% (95% CI: 13.1–33.1%) for all patients in FAS. The response rate in the platinum-sensitive and platinum-resistant groups was 27.3% (95% CI: 6.0–61.0%) and 21.0% (95% CI: 11.7–33.2%), respectively. Better response was obtained in patients with longer platinum-free interval when PLD was administered as second- or third-line chemotherapy. Clinical studies conducted in the US and Europe showed that the response rate of PLD was 28.4% in the platinum-sensitive group and 6.5–18.3% in the platinum-resistant group (11,12,13). These response rates were similar to those obtained in our trial.

Common adverse reactions reported in this study were haematological toxicities (leukopenia, neutropenia and decreased haemoglobin), HFS and stomatitis.

The median time to nadir for WBC, neutrophils and haemoglobin after the start of administration of PLD was 15–22 days, and the median time to recovery to baseline after reaching the nadir was 7–8 days. Repeated cycles did not lead to worsening the events. Most patients could receive PLD continually by concomitant use of G-CSF and dose modification, such as dose reduction and delay of next administration.

In the previous Phase III study (13), HFS and stomatitis occurred in 49% (Grade 3 or higher: 23%) and 40% (Grade 3 or higher: 8%) of patients, respectively. Although these toxicities were seen in 78.3 and 77.0% of patients in our study, only 16.2 and 8.1% of patients experienced Grade 3 or higher toxicities, respectively. Most patients could continually receive PLD treatment by dose modification of PLD and supportive care, and the patients discontinued due to toxicities were few.

Infusion-related reaction that is known as toxicity specific to PLD was seen in 14 patients (18.9%) during the first cycle, all of which were resolved on the day of the occurrence or the following day. The second cycle was administered in 11 of 14 patients with infusion-related reactions. No recurrence of infusion-related reactions was seen in all 11 patients. It is important to use PLD with close attention to the condition of patients at the first administration of PLD. Infusion-related reaction is related to the initial infusion rate of PLD. It has been reported that decreasing the infusion rate reduces the risk of the infusion-related reaction (21).

It has been reported that cardiac toxicity, which is a significant problem with the use of conventional doxorubicin, associated with PLD is mild (22). Also in this trial, all cardiac toxicities observed were Grade 1, and had no effect on continuation of the trial. Furthermore, no patients experienced Grade 2 or higher alopecia, and Grade 3 or higher gastrointestinal toxicities were rarely seen in our trial. These toxicities are frequently induced by treatment of conventional doxorubicin.

These results suggest that toxicity of PLD is manageable by dose modification of PLD and supportive care.

Most patients with ovarian carcinoma exhibited response to first-line chemotherapy, however, the incidence of recurrence is high and prognosis is poor. It might be important to recognize that the chemotherapy would be palliative treatment for treatment of recurrent ovarian carcinoma. PLD has a safety profile that is different from that of platinum and taxanes, which are used for the standard first-line chemotherapy. PLD has a low risk of enhancing cumulative toxicities (haematological toxicity or neurotoxicity) associated with first-line chemotherapy. PLD is expected to have a beneficial effect against disease progression as the proportion of patients with CR, PR or SD and time to progression were 60.3% and 166 days (median). Furthermore, PLD might make it easy to provide long-term outpatient chemotherapy since PLD would reduce a patient burden by dosing once every 4 weeks.

In conclusion, this trial demonstrated that PLD (50 mg/m^2 every 4 weeks) was expected to have antitumour effect in Japanese patients with Müllerian carcinoma previously treated with platinum-based chemotherapy and that toxicities associated with PLD are manageable by dose modification and supportive care. In the USA and Europe, combination chemotherapy with PLD and platinum has recently been investigated in the platinum-sensitive group where PLD is considered to be more effective (23,24,25). It is desirable to investigate the optimal regimen of the combination therapy in Japan.

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Conflict of interest statement

None declared.

References

1. Udagawa Y, Yaegashi Y. Ovarian Cancer Treatment Guideline. *Japan Society of Gynecologic Oncology*. 2nd edn. Tokyo: Kanehara & Co., Ltd 2007.
2. Markman M, Zaino RJ, Fleming PA, Gemignani ML. Carcinoma of the Fallopian Tube. In: Hoskins WJ, Perez CA, Young RC, Barakat R, Markman M, Randall M editors. *Principles and Practice of Gynecologic Oncology*. 4th edn. Philadelphia: Lippincott Williams & Wilkins 2004;1035–53.
3. Karlan BY, Markman MA, Eifel PJ. Ovarian Cancer, Peritoneal Carcinoma, and Fallopian Tube Carcinoma. In: Devita VT Jr, Hellman S, Rosenberg SA editors. *Cancer Principles & Practice of Oncology*. 7th edn. Philadelphia: Lippincott Williams & Wilkins 2005;1364–97.
4. Allen TM, Hansen C, Martin F, Redemann C, Yau-Young A. Liposomes containing synthetic lipid derivatives of poly (ethylene glycol) show prolonged circulation half-lives in vivo. *Biochim Biophys Acta* 1991;1066:29–36.
5. Jain RK. Vascular and interstitial barriers to delivery of therapeutic agents in tumors. *Cancer Metastasis Rev* 1990;9:253–66.

6. Woodle MC. Surface-modified liposomes: assessment and characterization for increased stability and prolonged blood circulation. *Chem Phys Lipids* 1993;64:249–62.
7. Needham D, McIntosh TJ, Lasic DD. Repulsive interactions and mechanical stability of polymer-grafted lipid membranes. *Biochim Biophys Acta* 1992;1108:40–8.
8. Huang SK, Martin FJ, Jay G, Vogel J, Papahadjopoulos D, Friend DS. Extravasation and transcytosis of liposomes in Kaposi's sarcoma-like dermal lesions of transgenic mice bearing the HIV tat gene. *Am J Pathol* 1993;143:10–4.
9. Huang SK, Lee KD, Hong K, Friend DS, Papahadjopoulos D. Microscopic localization of sterically stabilized liposomes in colon carcinoma-bearing mice. *Cancer Res* 1992;52:5135–43.
10. Muggia FM, Hainsworth JD, Jeffers S, Miller P, Groshen S, Tan M, et al. Phase II study of liposomal doxorubicin in refractory ovarian cancer: antitumor activity and toxicity modification by liposomal encapsulation. *J Clin Oncol* 1997;15:987–93.
11. Gordon AN, Granai CO, Rose PG, Hainsworth J, Lopez A, Weissman C, et al. Phase II study of liposomal doxorubicin in platinum- and paclitaxel-refractory epithelial ovarian cancer. *J Clin Oncol* 2000;18:3093–100.
12. Johnston SRD, Gore ME. Caelyx: phase II studies ovarian cancer. *Eur J Cancer* 2001;37(Suppl. 9):S8–14.
13. Gordon AN, Fleagle JT, Guthrie D, Parkin DE, Gore ME, Lacave AJ. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. *J Clin Oncol* 2001;19:3312–22.
14. Gordon AN, Tonda M, Sun S, Rackoff W. Long-term survival advantage for women treated with pegylated loposomal doxorubicin compared with topotecan in a phase 3 randomized study of recurrent and refractory epithelial ovarian cancer. *Gynecol Oncol* 2004;95:1–8.
15. O'Byrne KJ, Bliss P, Graham JD, Gerber J, Vasey PA, Khanna S, et al. A phase III study of Doxil/Caelyx versus paclitaxel in platinum-treated, taxane-naive relapsed ovarian cancer. *Proc Am Soc Clin Oncol* 2002;21:203a [Abstract 808].
16. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology™. Ovarian Cancer V.1.2008. Available from: http://www.nccn.org/professionals/physician_gls/PDF/ovarian.pdf.
17. National Cancer Institute. Ovarian Epithelial Cancer Treatment (PDQ®) Health Professional Version Recurrent or Persistent Ovarian Epithelial Cancer. Available from: http://www.cancer.gov/cancertopics/pdq/treatment/ovarianepithelial/HealthProfessional/page7.
18. National Institute for Health and Clinical Excellence. Ovarian cancer (advanced) - paclitaxel, pegylated liposomal doxorubicin hydrochloride and topotecan for second-line or subsequent treatment of advanced ovarian cancer. Available from: http://guidance.nice.org.uk/TA91.
19. Fujisaka Y, Horiike A, Shimizu T, Yamamoto N, Yamada Y'Tamura T. Phase 1 Clinical Study of Pegylated Liposomal Doxorubicin (JNS002) in Japanese Patients with Solid Tumors. *Jpn J Clin Oncol* 2006;36:768–74.
20. Mutch DG, Orlando M, Goss T, Teneriello MG, Gordon AN, McMeekin SD, et al. Randomized Phase III Trial of Gemcitabine Compared With Pegylated Liposomal Doxorubicin in Patients With Platinum-Resistant Ovarian Cancer. *J Clin Oncol* 2007;25:2811–8.
21. Chanan-Khan A, Szebeni J, Savay S, Liebes L, Rafique NM, Alving CR, et al. Complement activation following first exposure to pegylated liposomal doxorubicin (Doxil®): possible role in hypersensitivity reactions. *Ann Oncol* 2003;14:1430–7.
22. O'Brien MER, Wigler N, Inbar M, Rosso R, Grischke E, Santoro A, et al. Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYXTM/Doxil®) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. *Ann Oncol* 2004;15:440–9.
23. Ferrero JM, Weber B, Geay JF, Lepille D, Orfeuvre H, Combe M, et al. Second-line chemotherapy with pegylated liposomal doxorubicin and carboplatin is highly effective in patients with advanced ovarian cancer in late relapse: a GINECO phase II trial. *Ann Oncol* 2007;18:263–8.
24. du Bois A, Pfisterer J, Burchardi N, Loibl S, Huober J, Wimberger P, et al. Combination therapy with pegylated liposomal doxorubicin and carboplatin in gynecologic malignancies: A prospective phase II study of the Arbeitsgemeinschaft Gynäekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and Kommission Uterus (AGO-K-Ut). *Gynecol Oncol* 2007;107:518–25.
25. Alberts DS, Liu PY, Wilczynski SP, Clouser MC, Lopez AM, Michelin DP, et al. Randomized trial of pegylated liposomal doxorubicin (PLD) plus carboplatin versus carboplatin in platinum-sensitive (PS) patients with recurrent epithelial ovarian or peritoneal carcinoma after failure of initial platinum-based chemotherapy (Southwest Oncology Group Protocol S0200). *Gynecol Oncol* 2008;108:90–4.

クリニカルカンファレンス1　婦人科がんとTR

1）分子標的関連

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抗がん剤の歴史と分子標的薬

抗がん剤の歴史は1940年代にマスタードガスから応用されたナイトロジェンマスタードを初めてホジキン病の治療に用いたことから始まる．以後，がん化学療法は飛躍的進歩をとげ，不治の病とされてきた白血病も治癒ができるようになった．また，それまでは手術療法と放射線療法しか有効な治療手段がなかった固形癌も化学療法を組み合わせることによって治療成績の向上がみられるようになった．1960年代にはcyclophosphamideをはじめとするアルキル化剤が評価され，70年代には抗がん性抗生物質であるdoxorubicin，80年代にはcisplatinが登場し，90年代にはtaxane製剤，oxaliplatin，irinotecanなどの薬剤が登場し，治療成績の向上をもたらした．化学療法剤はわずか50年間で輝かしい進歩をとげたといえる．しかし，これまでの殺細胞効果だけを有する化学療法剤には効果，毒性の面で限界がある．21世紀になってから，細胞を核を攻撃し正常細胞にも影響を与えてしまう従来のcytotoxic drugと違って，癌細胞に特有に発現している増殖因子に対する抗体を作成しがんの増殖を抑制しようとする抗体療法や，シグナル伝達系の酵素を抑制する薬剤や，癌細胞の増殖に必要な血管新生を抑制する阻害剤などの分子標的薬の開発が盛んになってきている．その代表薬剤が，trastuzumab(ハーセプチン®)，rituximab(リツキサン®)，imatinib(グリベック®)，gefitinib(イレッサ®)などである．がん細胞に対する分子標的となるもの，また標的に対する分子標的薬を表1にまとめた．表に示すようにがん細胞の標的となる分子にはさまざまなものがあり，現在ではこれらの標的に対して，何百もの新規分子標的薬が開発され，臨床試験が開始されている．

分子標的薬を作用機序別に分類すると表2のように分類され，標的分子別に分類したものが，表3である．表4に現在，海外の第三相試験にて有効性が認められ，承認されている分子標的薬の一覧を示した．最近では，腎臓癌に対する分子標的薬の開発がめざましい．婦人科がんに対しては残念ながら，まだ第三相試験で有効とされた薬剤はなく，承認されていないのが現状である．

Molecular Targeted Therapy

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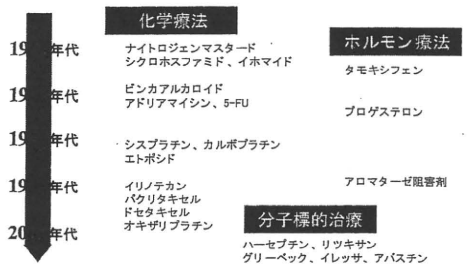
Key words: Targeted therapy · Molecular target chemotherapy

（表1） がん細胞の標的

分類	標的	分子標的薬
Growth Factor	Hormones EGF FGF PDGF	Hormone agonist/antagonist
Growth Factor Receptor	Cytokine receptor Tyrosine kinase	Anti-receptor antibody TK inhibitor Small molecule inhibitor
Intracellular Signaling Molecule	Farmesyltransferase Nonreceptor TKs MAP kinase JAK/STAT	Farmesyltransferase inhibitor Small molecule kinase inhibitor
Apoptosis	CDK Rb Akt	Apoptosis agonist
Oncogenesis	K-ras N-myc Bcl-2	Anti-sense oligonucleotide
Tumor Suppression	P53	Viral vectors
Angiogenesis and Metastasis	VEGF Rho B Matrix metalloproteinase Integrin	Angiostatin Endostatin Anti-VEGF Metalloproteinase inhibitor Collegnease
Immune System	T cell NK cell Macrophage Dendritic cell	Vaccine Monoclonal antibody CSF

抗がん剤の歴史



（図1）

（表2） 分子標的薬の分類（作用機序別）

■ Tyrosine kinase inhibitor：小分子化合物
Gefitinib (Iressa), Erlotinib (Tarceva)
Imatinib (Gleevec)
Sorafenib, Sunitinib, Temcirolimus, Lapatinib

■ Monoclonal antibody：大分子
Trastuzumab (Herceptin)
Rituximab (Rituxan)
Bevacizumab (Avastin)

（表3） 分子標的薬の分類（標的分子別）

■ EGFR
　Tyrosine kinase inhibitor：Gefitinib（Iressa），Erlotinib（Tarceva），Lapatinib
　Monoclonal antibody：Cetuximab（Erbitux）
■ HER2
　Monoclonal antibody：Trastuzumab（Herceptin）
■ Bcr-Abl, c-Kit
　Tyrosine kinase inhibitor：Imatinib（Gleevec）
■ VEGF-VEGFR
　Monoclonal antibody：Bevacizumab（Avastin）
　Tyrosine kinase inhibitor：Sorafenib, Sunitinib
■ CD20
　Monoclonal antibody：Rituximab（Rituxan）

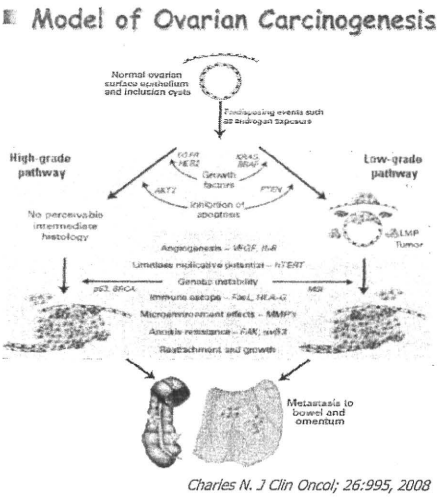
（表4） 悪性疾患に対する分子標的薬

Targeting agents for malignant disease		
Agents	Target	Indication
Imatinib (Gleevec®)	Bcr-Abl, c-Kit	CML, GIST
Trastuzmab (Herceptin®)	Her 2	Breast Cancer
Rituximab (Rituxan®)	CD20	B Cell Lymphoma
Bevacizumab (Avastin®)	VEGF	Colon Cancer, Lung cancer
Erlotinib (Tarceva®)	EGFR	Lung cancer, Pancreatic cancer
Cetuximab (Erbitux®)	EGFR	H&N cancer, Colon cancer
Sunitinib (Sutent®)	Multi target	GIST, Renal cancer
Solafenib (Nexavar®)	Multi target	Renal cancer
Temsirolimus (Torisel®)	mTOR	Renal cancer
Lapatinib (Tykerb®)	Her1, Her2	Breast cancer

卵巣癌に対する分子標的薬

卵巣癌の発生に関して，最近の論文で図2に示すようなpathwayが示されている[1]．すなわち，Low malignant potential(LMP)tumorになるべく，Low-grade pathwayと，通常の癌化に関連したHigh-grade pathwayである．High-grade pathwayには，EGFR，HER2，AKT2などの遺伝子が，Low-grade pathwayには，KRAS，BRAF，PTENなどの遺伝子が関わっている．また，その後の腫瘍の進展に，VEGF，IL-8，hTERT，FasL，HLA-G，MMP，FAK，αVβ3などの遺伝子が関わっているという．卵巣癌に対しても，これらの遺伝子をTargetとした分子標的治療が考えられる．これまでに卵巣癌に対して，表5に示すような薬剤の臨床試験が行われたが，このうち，Bryostatin，Trastuzumab，Gefitinibは効果が認められなかった．その他の薬剤に対しては，現在臨床試験が進行中である．CA125に対するモノクロナール抗体であるOregovomabはその効果が期待がされたが，卵巣癌術後，化学療法後の維持療法として，OregovomabとPlaceboとを比較したphase Ⅲ studyではOregovomabの有効性が証明されなかった[2]．

Erlotinib(Tarceva)はEGFR(epidermal growth factor receptor：上皮成長因子受容体)を分子標的とした選択的チロシンキナーゼ阻害剤である．チロシンキナーゼは細胞内のシグナル伝達の主役を担う細胞内の蛋白質のリン酸化活性に関与し，100種類以上存在，受容体型，非受容体型に分類される小分子化合物である．Erloinibは EGFR の ATP 活性化ドメインに結合し，ATP と競合し，自己リン酸化を阻害することでチロシンキナーゼ活性を阻害する．Erlotinibは，非小細胞性肺癌に対する RCT で生存期間延長効果をもたらしたため，2005年には，米国，欧州で承認，2007年に我が国でも承認されている．EFGR は卵巣癌に対しても，35～70％発現されているという報告があり，卵巣癌にも erlotinib の効果が期待できる．卵巣癌では，EGFR 陽性であることが確認された再発・難治症例34例を対象とした erlotinib 単剤投与による第Ⅱ相試験が行われ，2例(6％)で PR，15例(44％)で SD の結果であった[3]．他剤との併用投与では，カルボプラチン(＋パクリタキセル)との併用投与および Bevacizumab との併用投与が検討されている．Erlotinib＋bevacizumab 併用療法では，これまでに有害事象として消化管穿孔が高頻度であることが報告されており，慎重に判断していく必要がある[4]．また，初回標準治療後の維持療法として，erlotinib とプラセボ投与を比較する RCT が現在 EORTC で行われている(図3)．



Charles N. J Clin Oncol; 26:995, 2008

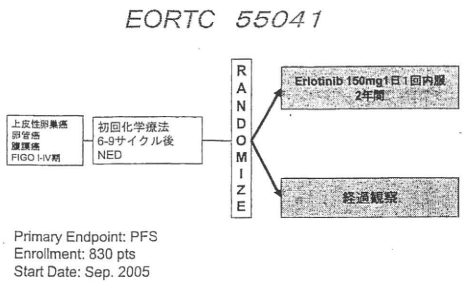
(図2)

卵巣癌に対する Bevacizumab

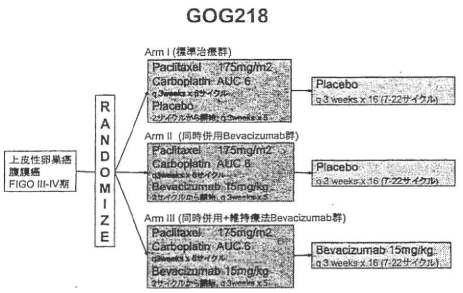
固形がんが浸潤や転移を起こす過程の一つに血管新生がある．微小環境では腫瘍細胞が

(表5)　Molecular Targeted Agents for Ovarian Cancer

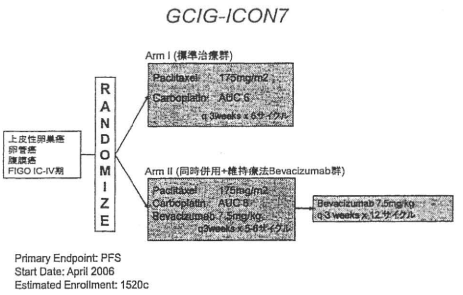
Agent	Target
Bortezomib	proteosome
Bevacizumab	VEGF-A
R115777	FTI
Lapatinib	EGFR/HER1, Her2
BAY 43-0006	Raf-1
Imatinib	C-kit/PDGFR
Pertuzumab	Her-2
Volociximab	VEGFR-1, 2, 3, PDGFR, c-kit
Sunitinib	PDGFR, c-kit, FLT-3
AMG-706	VEGFR-1,2,3, c-kit
Solafenib	Raf, VEGFR-2,3,FLT-3, c-kit, PDGFR
Temsirolimus	M-TOR
Enzastaurin	PKC-β
Erlotinib	EGFR



（図3）



（図4）



（図5）

糖たんぱくの一種であるVEGFなどの血管新生因子を放出することにより，血管新生シグナル経路が活性化する．このようにVEGFは腫瘍細胞が腫瘍周囲の間質へ増殖，移行，進展するのを促進する．Bevacizumabはマウス抗ヒトVEGFモノクローナル抗体のヒト組み換え型抗体であり，VEGFの働きを抑制する．いまだ明確ではないが，微小血管の増生を抑制し腫瘍の増殖を防ぐ，血管のnormalizationにより抗がん剤を有効に拡散させる，血管の成長や新生を防ぐことにより抗腫瘍効果を示すといった，いくつかの作用機序が考えられる．卵巣癌に対してVEGFの発現は，腹水産生，癌化，予後不良因子と関わっており，preclinical studyでは，anti-VEGF療法が腫瘍の増殖を抑制，悪性腹水を減少，化学療法との併用効果が証明されている[5]．

Bevacizumabは，大腸癌，非小細胞性肺癌については米国等，世界各国で承認されているが，卵巣癌については患者数が少なく経営的な判断から企業主導の臨床試験は海外でも実施されておらず，承認のある国はない現状である．しかし，既治療の治療抵抗性卵巣癌に対してBevacizmab単剤投与でも高い奏効率が得られていることから，その臨床導入は世界中から求められている．これまで再発・難治性卵巣癌に対して行われたBevacizumab単剤投与の第二相試験は米国から二つ報告[6][7]があり，奏効率18%（11/62人），16%（7/44人）と，Bevacizumab単剤による奏効率は固形癌の中で最も高かった．この結果から，現在，卵巣癌に対するBevacizumab投与の有用性を検討するために，ランダム化第三相比較試験が，2005年9月26日より米国GOGにより患者登録が開始されている（図4）．欧州ではICON7として，第三相試験が進められている．

国際共同医師主導治験としてのGOG218

GOG218は，予定症例集積期間3年である目標症例数2,000例にもかかわらず，2006年12月の時点で，221例の登録しか進んでおらず，試験参加がNCIより求められた．日本からも，企業治験で行うことを当初企業に打診したが，企業としては，日本でBevacizumabの卵巣癌に対する治験を行う予定が全くないということであった．今後，GOG218また，ヨーロッパでも計画されている卵巣癌に対するBevacizumabのランダム化比較試

験によって，Bevacizumabの有用性が証明された場合，試験が終了してから，改めて企業治験を開始した場合，他の薬剤と同様5～10年の日本での承認の遅れが予想されるため，医師主導治験として手続きを行い，日本から，GOG Japanのメンバー施設10施設が，GOG218へ参加することとした．2007年から準備を開始，NCI-CTEPとの治験薬輸入に関する協議，厚生労働省担当部署と治験薬搬送手続きについての協議，米国GOGミーティングに参加し，米国の研究者と国際共同臨床試験をどうやって進めていくかについて協議を行った．また，医師主導治験開始に際して，治験審査委員会に提出する書類作成として，GOG218プロトコール(英文)の和訳，説明同意文書(対訳版，意訳版)，標準業務手順書(医師主導治験取り扱い規定，治験審査委員会，自ら治験を実施する者，モニタリング，監査，被験者補償，治験薬取扱い，安全性情報取扱い，治験調整医師，効果・安全性評価委員会，治験薬概要書の作成，治験実施計画書の作成，説明同意文書)の作成を行った．その後，企業からの治験薬概要書の提供，企業への監査業務の委託契約，効果安全性評価委員会の設置・依頼，各施設での米国臨床試験に参加するための用件取得・書類提出(治験責任医師，治験分担医師のNCI investigator numberの取得，施設倫理審査委員長・倫理担当官・患者相談担当窓口・CRC・安全性業務担当者の倫理セミナーの受講)，効果安全性評価委員会の業務委託契約，などの作業を9月までに終了，9～10月の期間で，各施設にて，プロトコールの治験審査委員会への提出・承認を得た．平成19年11月6日独立行政法人医薬品医療機器総合機構へ治験届提出．現在，参加施設システム監査および各施設Kick-off meeting開始している．今後は，平成19年度12月初旬までに，NCIからの治験薬の搬送テストを実施し，安全に搬送可能であることを確認，各施設のシステム監査・Kick-off meeting終了，2008年3月31日現在までに4例の登録が進んでいる．

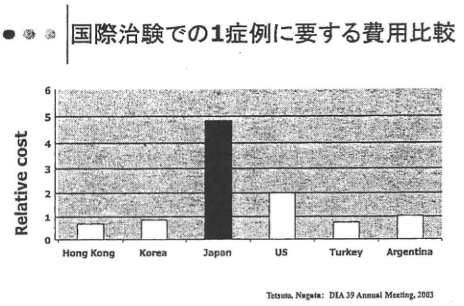
Drug Lagと日本

難治性卵巣癌の今後の方向性は，再発卵巣癌ではdoxil，topotecan，gemcitabineなどの薬剤が，進行卵巣癌では，bevacizumab，erlotinibなどが期待される薬剤である．上記のうち，doxilは既に世界80カ国で卵巣がん治療に承認されており，アジア地域で承認されていない国は，もはや北朝鮮民主主義人民共和国と日本くらいになってしまっている状況である．また，topotecanは世界70カ国以上で承認されており，gemcitabineは米国，欧州で承認されている．卵巣癌はchemo-sensitive tumorであるため，再発後も全身状態が良好で化学療法が奏効し，3rd line，4th lineと化学療法を続けながら，うまく癌と共存が望める癌種である．そういった状況でdoxil，topotecan，gemcitabineなどの薬剤が再発卵巣癌に対して保険適応上の問題で使用できない，治療オプションとして説明することができないことは，患者さんに大きな不利益をもたらすことと思わ

(表6) 世界初上市から各国上市までの平均期間

		承認製品数(1995-2005)	平均年数
1	米国	25	0.8
2	ドイツ	25	1.0
2	イギリス	23	1.0
2	カナダ	18	1.0
5	フランス	27	1.1
5	スイス	25	1.1
5	スウェーデン	24	1.1
8	オーストリア	24	1.2
8	デンマーク	22	1.2
10	フィンランド	23	1.3
10	オーストラリア	21	1.3
25	日本	14	3.4
	世界	28	1.6

れる[8]．世界と日本とのDrug Lagの問題は，Annals of Oncologyで取り上げられている[9]．この論文によると，67の抗がん剤を対象とした世界初上市から各国上市までの平均期間が主要先進国25カ国中，日本が最下位であり，平均3.4年かかっている(世界の平均は1.6年)(表6)．Drug Lagの原因としては，承認審査の遅れが取り上げられることが多いが，最近では，承認審査にかかる時間は海外と比べてそれほど遅れているわけではない[10]．むしろ日本における臨床試験/治験実施体制の不備，企業の日本からの治験離れ，治験開始の遅延，なども問題点としてあげられる．特に，治験がグローバル化している中で，日本の治験のコスト高は，外資系製薬企業から日本の薬剤開発が避けられる要因の一つとなっている(図6)．また，婦人科がんは罹患者数が他癌種よりも少ないため，企業治験の薬剤開発戦略からははずされることが多い．こうしたDrug Lagに対する対策としては，未承認薬剤に対しては，医師主導治験の促進，compassionate useの制度化，適応外薬剤に対しては，診療ガイドラインなどに記載されているような標準治療は保険支払基金で認可する制度へ(2007年9月卵巣癌に社会保険支払基金がエトポシド，子宮体癌にカルボプラチンを承認)，また，臨床試験での使用を保険支払基金が認容する制度へ(2008年4月より高度医療評価制度として開始)[11]，などの対策が必要と思われる．



(図6) 国際治験での1症例に要する費用比較(日本製薬工業協会長田徹人氏のスライドより引用)

《参考文献》

1. Landen CN Jr, Birrer MJ, Sood AK. Early Events in the Pathogenesis of Epithelial Ovarian Cancer. J Clin Oncol 2008 ; 26 : 995—1005
2. Berek JS, Taylor PT, Gordon A, et al. Randomized, Placebo-Controlled Study of Oregovomab for Consolidation of Clinical Remission in Patients With Advanced Ovarian Cancer. J Clin Oncol 2004 ; 22 : 3507—3516
3. Gordon AN, Finkler N, Edwards RP, et al. Efficacy and safety of erlotinib HCl, an epidermal growth factor receptor(HER1/EGFR)tyrosine kinase inhibitor, in patients with advanced ovarian carcinoma : results from a phase Ⅱ multicenter study. Int J Gynecol Cancer 2005 ; 15 : 785—792
4. Friberg G, Oza AM, Morgan RJ, Vokes EE, Gandara DR, Fleming GF. Bevacizumab(B)plus erlotinib(E)for patients(pts)with recurrent ovarian(OC)and fallopian tube(FT)cancer : Preliminary results of a multi-center phase Ⅱ trial. J Clin Oncol 2006 ; 24 : 5018
5. Burger RA. Experience With Bevacizumab in the Management of Epithelial Ovarian Cancer. J Clin Oncol 2007 ; 25 : 2902—2908
6. Burger RA, Sill MW, Monk BJ, Greer BE, Sorosky JI. Phase Ⅱ trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer : a Gynecologic Oncology Group Study. J Clin Oncol 2007 ; 25 : 5165—5171

7. Cannistra SA, Matulonis UA, Penson RT, et al. Phase Ⅱ study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. J Clin Oncol 2007; 25: 5180—5186
8. スマイリーホームページ. (Accessed at http://ransougan.e-ryouiku.net/drug_lag.html.)
9. Wilking N, Jonsson B. A global comparison regarding patient access to cancer drugs. Ann Oncol 2007; 18 Supple 3: iii1—iii82
10. 小野俊介, 安積織衛. 日本における新医薬品の承認審査期間. 政策研ニュース 2003; 12: 1—3
11. 厚生労働省高度医療評価制度について. (Accessed at http://www.mhlw.go.jp/topics/2008/04/tp0402-1.html.)

腫瘍内科，2(3)：220-225，2008

特集 国際共同臨床試験

米国多施設共同研究グループへの参加 1)医師の立場から*

勝俣範之**

Key Words：GOG, international clinical trial, bevacizumab

はじめに

がんの臨床試験が国際化(グローバル化)が進んできている理由として，①新規抗がん剤の開発が爆発的に進んでおり，より早く，より多くの患者を登録することが必要となった，②分子標的治療薬が台頭してくることによって，がん腫の中でもtargetがしぼられることになり，より多くの患者が必要となった，③稀少疾患に対する臨床試験の必要性が増してきた，などがあげられる．近年の国際共同試験の成果としては，一つの国際共同大規模臨床試験によって，全世界的に新たな標準治療が確立されるようになったことは，大きな成果と言えよう．

婦人科がん領域の国際共同試験

婦人科がん領域は，発生頻度が比較的稀であるため，研究者の数が多くないこともあり，国際協調性が以前より取られてきた．欧州ではEORTC(ヨーロッパ中心)(http://www.eortc.be/)，ICON(イギリス中心)のグループで国際共同試験が行われてきた．米国も巻き込んだ組織としては，Gynecologic Cancer Intergroup(GCIG)が1995年に創設され(http://ctep.cancer.gov/resources/gcig/index.html)，国際共同臨床研究を行っている．現在では16か国が参加しており，日本からは，婦人科悪性腫瘍化学療法研究機構〔Japanese Gynecologic Oncology Group：JGOG(http://jgog.gr.jp/)〕が参加しており，現在日本発の国際共同臨床試験である卵巣明細胞がんに対するCDDP＋CPT-11 vs. CBDCA＋Paclitaxelの臨床第III相試験(JGOG3017)が開始されており，すでに韓国が参加を表明，登録を開始，今後も英国，イタリアが参加予定である．

米国多施設共同試験グループ(Gynecologic Oncology Group：GOG)

米国GOGは，米国国立がん研究所(National Cancer Institute：NCI)スポンサーのがん臨床試験グループで米国で唯一の婦人科がんを対象とするグループである．GOGは1970年2月に設立された．研究費はNCIのがん研究費3,200億円(2006年，ちなみに日本のがん研究費の総額は2006年度は61億円)のうち，Cooperative Group Programに年間115億円費やされる．GOGは12のCancer Cooperative Groupの一つであり，年間の研究費は約15億である．これまで行われてきた臨床試験の数は461あり，現在のactive trialは55ある．GOGの組織構造を図1に示す．運営部門のofficeや統計センターなどが設置され，各がん種ごとの委員会が設置されている．Executive committeeとして，Data and Safety Monitoring Board(DSMB)は日本では効果・安全性評価委員会に

* Participation in American clinical trial group as a investigator.

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