Table 3 Costs

	Base case value	Range tested in sensitivity analyses
21-gene RT-PCR[a] assay (Oncotype DX[R] Breast Cancer Assay)	¥ 450,000	Change by ±50%
Adjuvant therapy		
Hormonal therapy, per year	¥ 534,610	Change by ±50%
Chemotherapy	¥ 343,001	Change by ±50%
Trastuzumab, per year	¥ 3,105,120	Change by ±50%
Treatment for toxicity		
Major	¥ 173,352	Change by ±50%
Monitoring		
After adjuvant therapy without recurrence, per year	¥ 25,340	Change by ±50%
Treatment for distant recurrence		
Hormonal therapy and chemotherapy, per year	¥ 558,458	Change by ±50%
Trastuzumab, per year	¥ 3,105,120	Change by ±50%
End-of-life, per year	¥ 1,315,143	Change by ±50%

[a] Reverse transcriptase-polymerase chain reaction

reflects other factor than medical judgements, for example, patients' and their family's preference. Therefore, we do not try to build care model of these cases but exercise an insurance claim review on 80 recent fatal cases in breast cancer at Tokyo Metropolitan Cancer and Infectious Disease Center Komagome Hospital. This results in ¥1,315,143 (US$11,436) per year, which is also used as the cost of treating fatal toxicity.

Costs are also discounted at a rate of 3% [32].

Comparison of scenarios

Incremental cost-effectiveness ratios (ICER) are calculated for the purpose of comparing the scenarios:

$$ICER = \frac{Cost_{RS-guided\_treatment} - Cost_{NCCN/St\_Gallen-guided\_treatment}}{Effect_{RS-guided\_treatment} - Effect_{NCCN/St\_Gallen-guided\_treatment}}$$

Sensitivity analysis

In order to appraise the stability of ICERs against assumptions and uncertainty of adopted values of probabilities, utility weights, and costs in our economic model, one way sensitivity analyses are performed. The age of cohort is changed to 45 and 65 years old. DFRS$_{10}$s shown in Table 1 are changed by ±50%, which embrace the relaxation of mid-value assumption of DRFS$_{10}$ of patients with intermediate risk according to St Gallen criteria into both end values. The use of adjuvant chemotherapy in NCCN-guided treatment is changed from 50% of high risk cases only to 100% of high risk cases and 50% of low risk cases; and from 0 to 100% of intermediate risk cases in St Gallen-guided treatment. Propensity to alter treatment among

patients classified as intermediate risk by RS criteria reclassification is changed from 100 to 50%. As shown in Table 2, probabilities other than relative risk reductions are changed by ±50%, while the relative risk reductions are changed according to the reported 95% confidence intervals of each value. The effectiveness of adjuvant trastuzumab is extended to 5 years. Utility weights are all changed by ±20%. And as shown in Table 3, costs are all changed by ±50%. Discount rate is also changed from 0 to 5%.

Budget impact estimation

Budget impact is defined as a forecast of rates of use (or changes in rates of use) with their consequent short- and medium-term effects on budgets and other resources to help health service managers [35]. The budget in this study is defined as funds held by social insurers. We estimate the budget impact with our economic model assuming that all new LN−, ER+, ESBC in Japan undergo RS-guided treatment instead of NCCN/St Gallen-guided treatment from 2008 to 2012. The incidence of breast cancer is adopted from a forecast [17], and a share of LN−, ER+, ESBC is fixed at 28.7% [16]. A share of the budget in costs is assumed to be 70% according to the co-payment ratio in Japan's social health insurance system.

Results

Cost-effectiveness

Table 4 shows the result of the cost-effective analysis. The cost of RS-guided treatment, ¥4,135,279 (US$35,959),

Table 4 Result of cost-effectiveness analysis

	Cost (¥)	Incremental cost (¥)	Effect (YOLS)	Incremental effect (YOLS)	Effect (QALY)	Incremental effect (QALY)	Incremental cost-effectiveness ratio	
							(¥/YOLS)	(¥/QALY)
NCCN[a]-guided treatment	3,845,923	–	19.812	–	19.309	–	–	–
vs. RS[b]-guided treatment	4,135,279[c]	289,355	19.895[c]	0.083	19.405[c]	0.097	3,465,713	2,997,495
St Gallen-guided treatment	3,841,580	–	19.679	–	19.173	–	–	–
vs. RS-guided treatment	4,134,791[c]	293,211	19.900[c]	0.221	19.410[c]	0.237	1,328,975	1,239,055

[a] National Comprehensive Cancer Network

[b] Recurrence Score

[c] The cost and effects of RS-guided treatment scenario are slightly different from each other in two comparisons because of the difference in the risk reclassification from counterpart scenarios

exceeds that of NCCN-guided treatment, ¥3,845,923 (US$33,443), which results in a positive incremental cost of ¥289,355 (US$2,516). The effect in YOLSs of RS-guided treatment, 19.895 years, exceeds that of NCCN-guided treatment, 19.812 years, which results in a positive incremental effect of 0.083 year. The effect in QALYs of RS-guided treatment, 19.405 years, exceeds that of NCCN-guided treatment, 19.309 years, which results in a positive incremental effect of 0.097 year.

Similarly, the cost of RS-guided treatment, ¥4,134,791 (US$35,955), exceeds that of St Gallen-guided treatment, ¥3,841,580 (US$33,405), which results in a positive incremental cost of ¥293,211 (US$2,550). The effect in YOLSs of RS-guided treatment, 19.900 years, exceeds that of St Gallen-guided treatment, 19.679 years which results in a positive incremental effect of 0.221 year. The effect in QALYs of RS-guided treatment, 19.410 years, exceeds that of St Gallen-guided treatment, 19.173 years, which results in a positive incremental effect of 0.237 year. The cost and effects of RS-guided treatment scenario in this comparison are slightly different from those in the former comparison because of a difference in the risk reclassification from counterpart scenarios.

In both comparisons, the routine use of the 21-gene RT-PCR assay gains more but costs more at the same time. Incremental cost-effectiveness ratios (ICERs) of the former comparison are 3,465,713 ¥/YOLS (30,137 US$/YOLS) and 2,997,495 ¥/QALY (26,065 US$/QALY), and those of the latter comparison are 1,328,975 ¥/YOLS (11,556 US$/YOLS) and 1,239,055 ¥/QALY (10,774 US$/QALY).

Stability of ICER

Figure 2 shows the results of one way sensitivity analyses. Items are listed in the order of the magnitude of ICER change in terms of yen per QALY, while those change ICER less than 200,000 ¥/QALY (1,739 US$/QALY) are not reported.

Between NCCN-guided treatment vs. RS-guided treatment, ICER is most sensitive to the change of the cost of

the 21-gene RT-PCR assay, which ranges from ¥672,402 (US$5,847) to ¥5,322,588 (US$46,283). It is also sensitive to the change of the utility weight for a health status after adjuvant therapy without distant recurrence, which ranges from ¥2,861,163 (US$24,880) to ¥5,725,775 (US$49,789). The changes of ICER by the change of all items fall in a range from ¥672,402 (US$5,847) to ¥5,725,775 (US$49,789). Among the values used in the outcome estimation, $DRFS_{10}$ of patients who are reclassified as intermediate risk by RS criteria from low risk by NCCN criteria, has the largest impact on the result. Among costs of treatments, the cost of adjuvant chemotherapy is most influential to the result.

Between St Gallen-guided treatment and RS-guided treatment, ICER is most sensitive to the change of the assumption on the use of adjuvant chemotherapy among patients classified as intermediate risk by St Gallen criteria, which ranges from ¥788,230 (US$6,854) to ¥2,989,020 (US$25,991). It is also sensitive to the change of the cost of the 21-gene RT-PCR assay, which ranges from ¥290,593 (US$2,527) to ¥2,187,518 (US$19,022). The changes of ICER by the change of all items fall in a range from ¥290,593 (US$2,527) to ¥2,989,020 (US$25,991). Among values used in the outcome estimation, $DRFS_{10}$ of patients who are reclassified as high risk by RS criteria from intermediate risk by St Gallen criteria, has the largest impact on the result. Among costs of treatments, the cost of adjuvant chemotherapy is most influential to the result.

Overall, the change of ICERs by the change of assumptions and values is limited from ¥290,593 (US$2,527) to ¥5,725,775 (US$49,789).

Budget impact

Table 5 shows the result of the budget impact estimation. Annual costs per case by the scenario are calculated from our economic model. RS-guided treatment accompanies high costs in the first year, which probably reflects that the
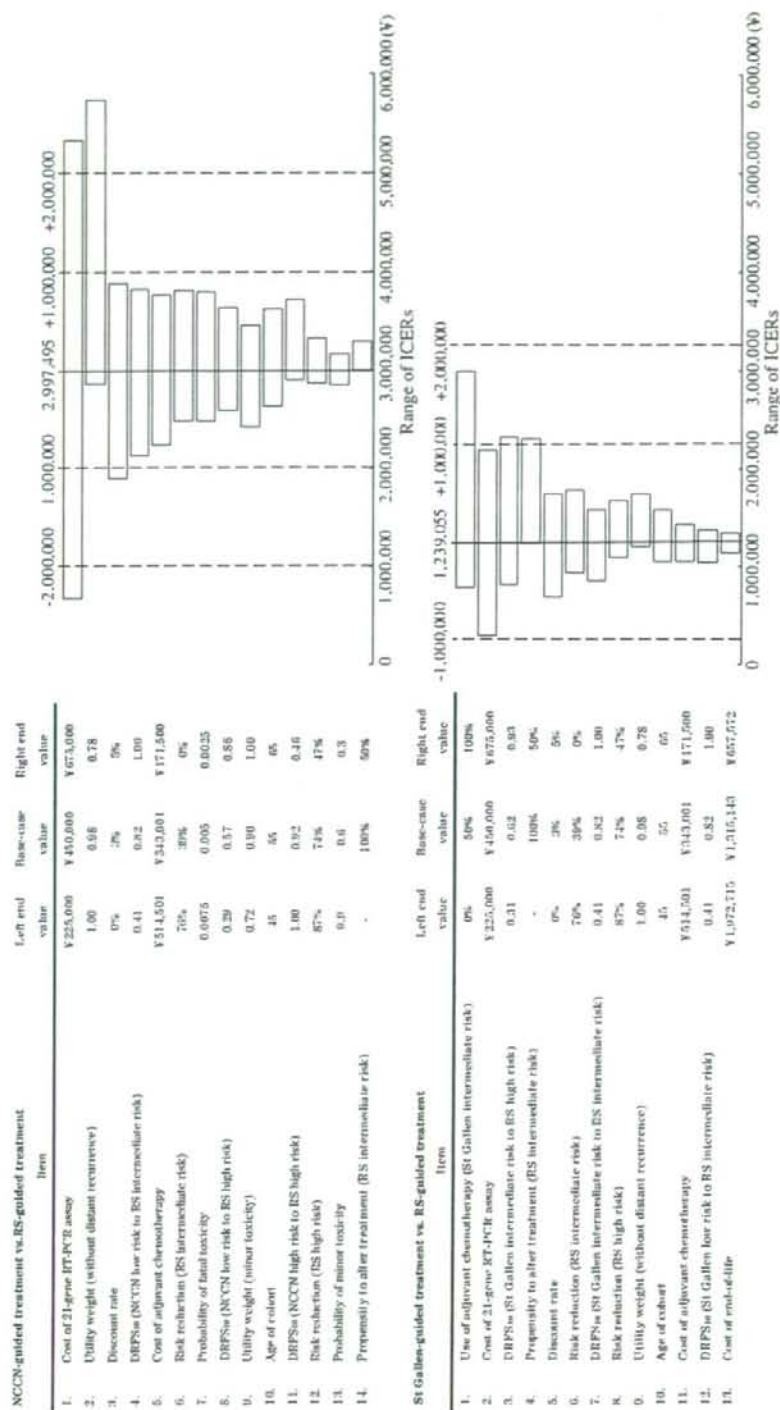
Fig. 2 Results of sensitivity analyses. Abbreviations: National Comprehensive Cancer Network (NCCN), reverse transcriptase-polymerase chain reaction (RT-PCR), recurrence score (RS), distant recurrence free survival in 10 years (DRFS$_{10}$) incremental cost-effectiveness ratio (ICER)

Table 5 Result of budget impact estimation

1. Annual cost per case

		First year	Second year	Third year	Fourth year	Fifth year
NCCN[a]-guided treatment vs. RS[b]-guided treatment	NCCN-guided treatment	¥1,677,915	¥535,596	¥541,683	¥548,444	¥579,241
	RS-guided treatment	¥1,976,790	¥536,596	¥542,448	¥548,958	¥579,614
St Gallen-guided treatment vs. RS-guided treatment	St Gallen-guided treatment	¥1,657,096	¥536,637	¥543,647	¥551,397	¥582,994
	RS-guided treatment	¥2,002,128	¥536,594	¥542,439	¥548,939	¥579,581

2. Annual incidence

	2008	2009	2010	2011	2012
Incidence of breast cancer	43,939	44,754	45,569	46,150	46,731
Incidence of LN−, ER+, ESBC	12,610	12,844	13,078	13,245	13,412

3. Budget impact estimation

		2008	2009	2010	2011	2012
NCCN-guided treatment vs. RS-guided treatment	Cost of NCCN-guided treatment	¥21,158 million	¥28,274 million	¥35,572 million	¥42,937 million	¥50,733 million
	Cost of RS-guided treatment	¥24,927 million	¥32,140 million	¥39,553 million	¥46,972 million	¥54,844 million
	Incremental cost	¥3,769 million	¥3,866 million	¥3,961 million	¥4,035 million	¥4,111 million
	Budget impact	¥2,638 million	¥2,706 million	¥2,773 million	¥2,825 million	¥2,877 million
St Gallen-guided treatment vs. RS-guided treatment	Cost of St Gallen-guided treatment	¥20,856 million	¥28,025 million	¥35,346 million	¥42,743 million	¥50,576 million
	Cost of RS-guided treatment	¥25,247 million	¥32,465 million	¥39,845 million	¥47,307 million	¥55,183 million
	Incremental cost	¥4,351 million	¥4,440 million	¥4,518 million	¥4,546 million	¥4,607 million
	Budget impact	¥3,046 million	¥3,108 million	¥3,163 million	¥3,195 million	¥3,225 million

[a] National Comprehensive Cancer Network

[b] Recurrence Score

high price of the 21-gene RT-PCR assay is not cancelled out by the reduction of adjuvant chemotherapy.

Costs treating LN−, ER+, ESBC incidence with NCCN/St Gallen/RS-guided treatment are calculated by the year taking mortality into account, and incremental costs are also calculated by the year according to comparisons. Calculated with these costs, the budget impact of the diffusion of the assay in Japan is estimated as ¥2,638 million (US$23 million) to ¥3,225 million (US$28 million).

Discussion

We evaluate the cost-effectiveness of the 21-gene RT-PCR assay in Japan's health care system with two scenarios depicting status quo and one scenario of the routine use of the assay for LN−, ER+, ESBC. Our economic model indicates that the diffusion of the assay gains more in terms of outcome but costs more at the same time. The estimated ICERs, 2,997,495 ¥/QALY (26,065 US$/QALY) and 1,239,055 ¥/QALY (10,774 US$/QALY), comparing NCCN/St Gallen-guided treatment with RS-guided treatment, respectively, are not more than a suggested social willingness-to-pay for one life year gain from an innovative medical intervention in Japan, 6,000,000 ¥/QALY (52,174 US$/QALY) [36]. Sensitivity analyses show that this result is plausibly robust, since ICERs do not exceed the threshold by various changes of assumptions made or values employed. In this sense, the assay has good value for money.

Incremental effects in terms of QALY are longer than those in terms of YOLS; and ICERs in terms of yen per QALY are smaller than those in terms of yen per YOLS in both comparisons. These imply that the assay is not only efficient in prolonging survival but also improving quality of life.

Our sensitivity analyses also reveal that the price of the assay is one of the major determinants of cost-effectiveness as expected. An intuitive comparison with the price of a conventional gene diagnosis test of malignant tumour in Japan, ¥450,000 (US$3,913) vs. ¥20,000 (US$174), seems to make a health manager feel it difficult to reimburse the cost of the assay by the social insurance, because there may be an incompatibility to an incremental manner of revising fee schedule. Our study, however, implies that the price offered by Japanese supplier of Oncotype DX® Breast Cancer Assay still makes ICER an acceptable level from the viewpoint of welfare economics.

We estimate the budget impact of the assay on the social health insurance system. The policy implication of the budget impact is not prescriptive [37]. Yet, the estimated impact, ¥2,638 million (US$23 million) to ¥3,225 million (US$28 million) per year for the coming 5 years, is

substantially less than the estimated budget impact of adjuvant trastuzumab, which is about to be included into social insurance benefit, ¥16,000 million (US$139 million) to ¥32,000 million (US$278 million) [38]. The characteristics of the assay of which application is limited to only once per case probably contribute to this difference, since the cost of trastuzumab amounts through its repeated administration. This implies that the diffusion of the assay through listing as an approved diagnostic test by the social health insurance could be justifiable.

The past economic evaluation of the assay reported from the U.S. considers a change from NCCN-guided treatment to RS-guided treatment [19], while our model allows a comparison between NCCN-guided treatment and St Gallen-guided treatment as an ex ante scenario. We find a notable difference in ICERs in this comparison. The ICER of the change from St Gallen-guided treatment is more favourable than that from NCCN-guided treatment. This is interesting because the reduction of use of adjuvant chemotherapy according to the reclassification from St Gallen criteria, 26%, is smaller than that from NCCN, 43%. The difference in ICER is due to more gain in the outcome. Although caution is needed in transferring the findings from economic models to any different context [39], our model might indicate that the assay has better value for money in countries where St Gallen-guided treatment is widely used.

However, this study has its own limitations. First, our outcome estimation depends on the validation studies carried out in the U.S. Although the evidences adopted are considered as the best available knowledge, it is needless to say that there are differences in population, as well as in cancer care practice between the U.S. and Japan. With this in regard, another validation study employing Japanese historical clinical trial data with the gene assay of preserved tumour tissue is launched [40]. A further economic evaluation incorporating new evidences is necessary to confirm the findings of this study. Second, utility weights adopted here are also derived from Western countries due to an unavailability of data from Japan. Third, our model does not include potentially costly clinical stages such as local recurrence or contralateral breast cancer due to the lack of data in validation studies. Regarding these shortcomings, reports and data that refines the model are awaited. Fourth, consensus guidelines are renewed continuously by incorporating newly available evidences [11, 41], so that the relative usefulness of the assay may be diminished in the near future, or the assay may be incorporated in the guidelines in a long run.

The use of the 21-gene RT-PCR assay has just begun to have an impact on clinical recommendations made by the U.S. oncologists and patients' choice [42]. It is easy to imagine that similar change in practice will occur in Japan

soon, because patients have strong preference to innovation such as tailor-made medicine [1]. As the prognostic usefulness of the 21-gene RT-PCR assay in guiding treatment for lymph-node-positive cases is recently reported [43], the indication of the assay will expand. Further economic evaluation that responds to this contextual change may become imperative.

Once the usefulness of the assay is confirmed by the Japanese validation study, Japanese health manager inevitably needs to decide how to fit the assay to the health care system. The results of this study imply the possibility of coverage by the social insurance. If health manager gives much importance to fiscal policy or cost containment, the selective indication of the assay for higher risk patients, which results to avoid additional use of adjuvant chemotherapy, might be a potential option. Further analysis incorporating such scenarios may be useful.

In conclusion, the routine use of the 21-gene RT-PCR assay for LN−, ER+, ESBC is indicated as cost-effective with a fundable level of budget impact in Japan. The results could inform health managers in developed countries where NCCN-guided treatment as well as St Gallen-guided treatment are practiced.

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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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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/m² 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/m² 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/m² 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 ≤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 ≤1.5 mg/dl; and (vi) other adverse drug reactions ≤ 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/m²) for the next cycle: (i) HFS or stomatitis ≥ Grade 3; (ii) neutrophil count <500/mm³ or WBC count <1000/mm³ that was maintained for at least 7 days; (iii) neutrophil counts <1000/mm³ with 38.0°C or higher fever; (iv) platelet reduction <2.5 × 10⁴/mm³; (v) other adverse drug reactions ≥ 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/mm³ with fever (≥38°C); (ii) neutrophil counts <500/mm³; (iii) experience of either (i) or (ii) in the prior cycle and neutrophil counts <1000/mm³ 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 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/m² 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.
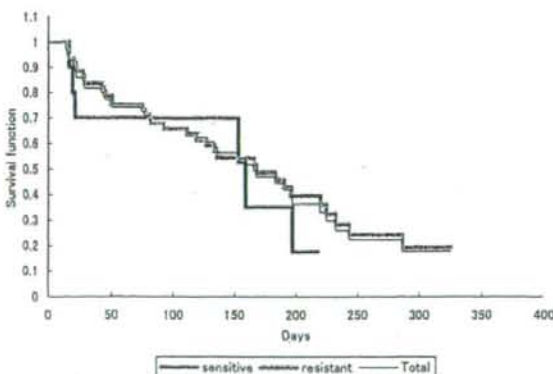
Table 4. Grades 3 and 4 adverse drug reactions

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.

Conflict of interest statement

None declared.

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放射線治療，外科的治療を依頼する病態とタイミング

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■ ポイント

● がんはどんな場所にも転移・浸潤し，さまざまな症状や病態を引き起こすため，それに対応するには他科の医師と医療連携をとりながら診療していく必要がある．

● 特に oncologic emergency では緊急対処が必要であり，適切な診断のもとで早急に処置しなければならない．

● 治療法の選択については転移巣の個数や大きさだけでなく，その患者の予後や全身状態もかかわってくるので，それらを考慮のうえで適切に判断しなければならない．

がんの診療を行っていくなかで，我々はさまざまな病態に直面する．oncologic emergency と呼ばれる緊急処置を必要とする病態をはじめ，内科医の力だけでは限界がある場面に直面する場合がある．こうした状況において外科医，放射線治療医，intervension radiology（IVR）を専門とする医師，また内科でも循環器内科医や呼吸器内科医達の協力を得ながら治療を行う必要がある．

本稿では他科医にコンサルトする病態について解説する．

oncologic emergency

がんが原因で緊急対応を必要とする病態で，主なものには上大静脈症候群，気道狭窄，脳転移，脊髄圧迫，胸水，心嚢水，高カルシウム血症などが挙げられる．これらは oncologic emergency と呼ばれ，生命を脅かす危機的な状況に対して，適切な判断と処置が必要とされる．

■ 脊髄圧迫

悪性腫瘍による脊髄圧迫は，腫瘍の転移による合併症のなかで最も早期診断，治療開始を必要とする病態の一つである．椎体への転移，脊髄への転移・浸潤は一般に血行性転移であり，脊髄圧迫の原因となる悪性腫瘍としては，乳癌，肺癌，前立腺癌などが多い．症状として背部痛が神経症状に先行して出現し，その後，対麻痺，四肢麻痺，知覚障害，膀胱直腸障害を認める例が多い．

脊髄圧迫を疑う場合，脊椎の単純 X 線撮影と神経根症状と組み合わせて約 80％の症例で診断可能である．近年，MRI の普及に伴い，局剤診断や部位診断が正確に行えるようになってきた．そのため，治療方針や治療範囲の決定のために MRI 検査を行うことが望ましい．治療については別項に譲るが，多くの場合，副腎皮質ホルモンを投与しながら放射線治療や手術が施行される．

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治療開始までの期間が遅れると，機能温存率は低下するため早期の治療が大切である．3カ月以上の予後が予想され，麻痺症状が発症してから48時間以内，脊髄圧迫症状が1カ所のみの転移性悪性腫瘍による脊髄圧迫症状の患者を対象とした「手術＋放射線治療」と「放射線治療単独」との比較試験があり，手術と放射線治療の併用療法のほうが優れていたという報告もある．そのため発症時には患者の全身状態および骨転移・圧迫の状態を精査して整形外科医や放射線治療医と早急に連携をとりながら適切な治療法を選択していくことが重要である．

■ 脳転移

脳はがんが転移を起こす場所としては好発部位であり，多くの場合，臨床的に問題となるさまざまな神経症状を引き起こす．主な症状としては頭痛，嘔吐，運動機能障害，痙攣，精神機能障害などが挙げられ，数日から数週間で進行する例が多い．時に脳転移病巣からの出血で急激に症状が現れたりする場合も存在する．症状緩和目的で副腎皮質ホルモンや痙攣発作を伴う場合には抗痙攣薬を用いる．

脳転移に対する治療としては，主として放射線治療(radiosurgery, whole brain radiotherapy)や手術となる．その適応については，脳転移病巣の数，大きさ，部位，全身状態，症状によって決まる．多発脳転移ですべてを切除不能であっても，症状の責任病巣を切除する目的で手術を行う場合もあり，こうした適応について脳外科医と放射線治療医と連携しながら治療を決定していく．

■ 上大静脈症候群

上大静脈症候群(superior vena cava syndrome：SVCS)は上大静脈の圧迫，浸潤，閉塞によって血流の通過障害をきたす病態である．原因として非腫瘍性疾患(炎症性疾患，血

栓症，大動脈瘤など)でも起こしうるが，そのほとんどが悪性疾患である．疾患として肺癌，悪性リンパ腫が多く，その両者で70％を占めるとされる．症状として呼吸困難，上肢，顔面の浮腫，チアノーゼ，咳嗽，胸痛，頭重感などをきたし，頭頸部，上肢，胸壁体表の血管の怒張を認める．

多くの場合，胸部X線写真の所見と身体所見で診断可能であるが，腫瘍の周辺臓器への拡がり，閉塞の程度，血栓症の有無，側副血行路の評価のため可能であれば両側上肢より造影CTを行う．

悪性疾患に伴う上大静脈の閉塞は腫瘍の増大とともに週単位で進行し，側副血行路が代償できず症状が重篤になる場合がある．悪性リンパ腫，小細胞肺癌，胚細胞腫瘍といった化学療法に対する感受性の高い腫瘍では，上大静脈症候群を合併していても治癒の可能性があり，病期に応じた治療を行う．また，未治療非小細胞肺癌の場合，症状緩和目的の化学療法および放射線治療による症状緩和率はそれぞれ59％と63％と報告されている．化学療法抵抗性あるいは前治療のため治療抵抗性を獲得している場合，放射線治療による症状緩和率は小細胞肺癌で62〜80％，非小細胞肺癌で46％と報告されている．血管内ステントについては，早期に症状緩和が達成されたとする報告が存在する．しかし，いずれも少数例の後ろ向き試験で，ステント挿入の場合には狭窄範囲の狭い症例のみを選択している可能性もあり，ステントによる有効性については確固たるものではなく，また合併症も考慮して適応を決める必要がある．腫瘍の性質，腫瘍の増大速度，身体状態に応じて放射線治療医，IVR医と連携をとりながら治療方針を決定する．

■ 気道狭窄

腫瘍の増殖・浸潤により中枢気道周囲の圧

迫・狭窄をきたし呼吸不全となる．原因として気管支原性肺癌や食道癌の直接浸潤が多い．症状として呼吸困難，呼吸音減弱，喘鳴，咳，痰，チアノーゼなどの症状を呈するが，危機的な状況になり初めて症状や理学所見を伴う例が多く，迅速な診断が必要である．胸部単純X線写真で気道周囲の腫瘍性病変の確認は可能であるが，中枢気道閉塞の診断は困難な場合が多く，胸部CT検査や気管支鏡検査を行って気道狭窄の有無，程度，範囲などを評価する．

　化学療法，放射線治療に感受性の高い腫瘍で狭窄が軽度の場合は，原疾患に対する治療を優先する．狭窄が高度で急速に進行している場合は気管支インターベンションが適応となる．気管支インターベンションについて大規模な比較試験はなく標準治療とされるものはないが，治療により狭窄が解除され救命できたという報告が多数あり，状況に応じて治療法を選択する必要がある．そのため，上記症状が出現している場合や画像検査上で気管狭窄をきたしそうな場合には，呼吸器内科医や放射線治療医との連携が必要である．

■ 心嚢水/心タンポナーデ

　心嚢水貯留により心臓の拡張障害が起こり心拍出量が減少し，循環不全をきたす．大量の心嚢水貯留や，少量でも急激に心嚢水が貯留すると心タンポナーデとなり生命の危機を生じる状況となる．悪性疾患に伴う心嚢水貯留は亜急性の経過をとる場合が多く，時に無症状であったり，胸部不快，軽度の呼吸苦，倦怠感を訴える程度のこともある．急激に心タンポナーデに至った場合は胸痛，呼吸困難，意識障害など重篤な症状を呈する．身体所見として頸静脈怒張，肝腫大，奇脈，頻脈，低血圧，脈圧減少，チアノーゼ，尿量減少などがみられる．

　胸部単純X線写真は心陰影の拡大など，大量に貯留した場合，診断に結びつく場合もある

が感度は低い．無症候性の場合は経過観察中のCTで発見される場合もある．心タンポナーデを疑う場合は，まず心臓超音波検査を行い，心嚢水の有無，局在，量，心膜の状態など得られる情報も多く，また緊急を要する場合は，そのまま循環器内科医やIVR医のサポートの下で心嚢穿刺などの治療にも移行できる．一部に癒着などで穿刺が困難な状況では，開胸下にドレナージを行う場合もある．

▌転移巣手術の適応

　近年の技術の進歩と安全性の向上により，転移肝腫瘍や転移性肺腫瘍に対しても積極的な転移巣の切除が試みられてきた．その結果，一部の悪性腫瘍では切除により治癒や延命を期待できることが明らかになってきた．

　転移性肝腫瘍の場合，特に大腸癌でその有用性が示され，原発巣から門脈にのって肝に転移巣を形成し，肝にとどまる時期を経て肝静脈系から肺へと転移するカスケード理論が提唱されており，肝切除をすれば治癒の可能性がある．

　転移性肺腫瘍の場合，卵巣癌，胚細胞腫瘍，絨毛癌，骨肉腫，Ewing肉腫，大腸癌では肺切除によって治癒や延命を期待される．胚細胞腫瘍，絨毛，骨肉腫，Ewing肉腫などは化学療法を行った後に，画像検査で評価して切除可能かを決定する．

　こうした転移巣を切除する条件としては，原発巣がコントロールされていること，肝あるいは肺に限局的，病変が切除可能であることが挙げられる．転移個数は単発に対して多発のほうが予後不良であるが，転移巣が何個まで切除すべきかはコンセンサスが得られておらず，施設間での違いも大きいのが現状である．

骨転移の治療

　腫瘍が骨に転移することで骨痛，病的骨折，神経麻痺，高カルシウム血症などが引き起こされる．骨転移に対する治療は主には放射線治療，手術，薬物療法があるが，それらの目標は骨合併症を減らし患者のQOLを改善させることである．

　骨転移に対する放射線治療は痛みの軽減，病的骨折の予防，麻痺の予防効果がある．痛みが強い場合や骨折を起こしそうな場合，神経症状

がある場合には，すぐに放射線治療医と相談が必要である．外科的治療としては長管骨の骨折時や骨折予防目的で手術を行う場合がある．薬物療法としては骨合併症の頻度を減らす目的でビスホスホネート製剤の投与や，強い骨痛に対してはWHO 3段階除痛ラダーに従って鎮痛薬を適切に投与する．しかし，薬物療法に反応しない疼痛で，他の治療法が適切でない場合には，鎮痛補助薬の導入や硬膜外ブロックなどによる除痛の適応について緩和ケア医や麻酔科医と相談して，患者のQOL改善に努める．

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特集　変貌する感染症