expensive procedures, such as surgery. Future studies should evaluate the accuracy of this prediction model in a larger cohort or non-Japanese cohort, and whether the clinical decisions made based on the prediction model actually improve clinical outcomes.

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ORIGINAL PAPER

Prognostic factors for malignant pericardial effusion treated by pericardial drainage in solid-malignancy patients

Kan Yonemori · Hideo Kunitoh · Koji Tsuta · Tetsutaro Tamura · Yasuaki Arai · Yasuhiro Shimada · Yasuhiro Fujiwara · Yuko Sasajima · Hisao Asamura · Tomohide Tamura

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Abstract

Purpose Malignant pericardial effusion is a frequent complication of advanced incurable malignancies and requires treatment. The purpose of this study was to identify prognostic factors for cytology-positive malignant pericardial effusion in patients treated by pericardial drainage.

Methods We retrospectively analyzed a series of consecutive patients diagnosed with cytologically positive malignant pericardial effusion who were treated by pericardial drainage at the National Cancer Center Hospital, Tokyo.

Results A total of 88 patients with pericardial effusion were treated by pericardial drainage, 60 patients were diagnosed with cytological positive malignant pericardial effusion including 32 with non-small cell lung cancer, 13 with breast cancer, 8 with gastrointestinal cancer, and 7 with miscellaneous cancers. Subxiphoid pericardiostomy was performed in 50 of the patients and percutaneous tube pericardiostomy in the other 10 patients. Malignant pericardial effusion recurred in 14 patients, and pericardial drainage was performed again in 9 of them. The median overall survival time was 6.1 months, and the 1-year survival rate was 28%. A multivariate analysis revealed the following significant negative prognostic factors: performance status, development of malignant pericardial effusion during chemotherapy, mediastinal lymph node enlargement, and cytologic type. ($P = 0.03$, 0.02, 0.01, 0.001, respectively).

Conclusion Patients with poor prognostic factors may be better to consider as indication of palliative therapy, even if oncologic emergency had been resolved rapidly by drainage.

Keywords Oncologic emergency · Malignant pericardial effusion · Drainage · Supportive care · Prognostic factor

K. Yonemori (✉) · H. Kunitoh · Y. Fujiwara · T. Tamura
Division of Medical Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
e-mail: kyonemor@ncc.go.jp

K. Tsuta · Y. Sasajima
Division of Clinical laboratory, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

T. Tamura
Division of Cardiology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

Y. Arai
Division of Diagnostic Radiology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

H. Asamura
Division of Thoracic Surgery, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

Y. Shimada
Division of Gastrointesinal Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

Introduction

Although metastatic involvement of the heart and pericardium is found at autopsy in 8.5–21% of patients who have died from a malignant tumor, it is detected in a much smaller percentage clinically [1, 2]. The most common cancer involving the pericardium are lung cancer, breast cancer, esophageal cancer, lymphoma, and leukemia [3, 4].

The majority of patients with pericardial effusion are asymptomatic and previous study showed that pericardial effusions less than 10 mm on an echocardiogram may be

an incidental finding and asymptomatic [2, 5]. The consequences of pericardial effusion mainly depend on the rate of exudation, compliance of the pericardium, and fluid volume. When malignant pericardial effusion (MPCE) occurs with symptoms of hemodynamic compromise either as an acute emergency or with insidious development of symptoms, prompt diagnosis, and treatment result in palliation and significant prolongation of survival time.

The overall survival time of MPCE patients has generally been short, ranging from 2 to 5.6 months [6–11]. The management and clinical course of MPCE depend on many factors, such as the underlying medical status of patient and the extent and type of the underlying malignant disease. To our knowledge there have been only a few reports describing prognostic factors in patients with MPCE [8–12]. The design of the studies may not have been entirely appropriate, however, because the analyses of prognostic factors included comparing patients with cytopathology-negative pericardial effusion or MPCE patients with patients with pericardial effusions of benign etiology [8–12]. Therefore, these study properly concluded patients with cancer-related or cytology positive MPCE was poor prognosis compared with patients with pericardial effusion of benign etiology [9, 11, 12].

In the present study we retrospectively analyzed the predictive factor for MPCE recurrence and the prognostic factors for cytology-positive MPCE in a series of consecutive solid-cancer patients treated with MPCE by pericardial drainage.

Patients and methods

Patients

A total of 88 patients with pericardial effusion were treated by pericardial drainage (subxiphoid pericardiostomy or percutaneous pericardiostomy) between February 1998 and November 2005 at the National Cancer Center Hospital, Tokyo. Of these, 60 patients were diagnosed with cytology-positive MPCE. The baseline investigation of the patients included a history and physical examination, chest computed tomography, and electrocardiography. Trans-thoracic echocardiography was performed by a cardiologist (T.T.).

Subxiphoid pericardiostomy was performed by making a small vertical incision extending 4–6 cm inferiorly from the xiphoid process. The anterior pericardium was identified, and a piece of pericardium 2–4 cm in diameter was removed. The pericardial sac was drained with a 20–24 Fr silicone tube. Percutaneous tube pericardiostomy was performed by inserting an 8 Fr tube percutaneously via a subxiphoid approach into the pericardial sac and then using the Seldinger technique. Both procedures were performed under local anesthesia. The tubes were positioned to allow drainage by gravity, and they were suctioned or flushed as necessary. The pericardial effusion obtained was routinely submitted for bacterial culture, the results were negative in every case. When the volume of drained pericardial fluid decreased to 25 ml or less per day, the drainage tube was removed. Sclerotherapy by pericardial instillation of a sclerosing agent was performed at the discretion of the attending physician.

Evaluation and statistical analysis

Recurrence of MPCE was defined as progression based on radiographic or echocardiographic examination after removing pericardial drainage tube. Overall survival time was measured from the first day of pericardial drainage until death.

We analyzed predictive factors for recurrence of MPCE by univariate analysis (Pearson chi-square test/Fisher exact test). The clinical variables before pericardial drainage were chosen by considering possible factors based on previous studies and our experience [8–12]. At the time of the pericardial drainage for MPCE, 12 categorical pretreatment variables were selected for statistical analysis: gender (male versus female), age (<60 versus 60 ≤), disease (lung cancer versus other), cytologic type (adenocarcinoma versus other), performance status (≥3 versus 3>), number of metastatic site (≥4 versus 4>), mediastinal lymph node enlargement (present versus absent), pleural effusion (present versus absent), MPCE at the time of diagnosis (present versus absent), malignancy recurred in MPCE (yes versus no), occurrence of MPCE during chemotherapy (yes versus no), and any prior history of chemotherapy (yes versus no). Median overall survival was estimated by the Kaplan–Meier method, and the survival analyses were assessed by the log-rank test. Cox's proportional hazards model according to a stepwise procedure was used to evaluate prognostic factors that were significantly related to survival. The statistical analyses were performed with SPSS 12.0 J software (SPSS Inc., Chicago, IL), and differences were considered significant at a P value <0.05 (two-sided).

Results

The background of the 60 patients is summarized in Table 1. The underlying disease was non-small cell lung cancer in 32 patients, breast cancer in 13 patients, esophageal cancer in 6 patients, small-cell lung cancer, and gynecological cancer in 2 patients each, and gastric cancer,

Table 1 Patient backgrounds

No. of Patients	60
Male/female	30/30
Median age (range)	58 (32–72)
Performance status	2 (1–4)
Disease	
Non-small cell lung cancer	32
Breast cancer	13
Esophageal cancer	6
Small cell lung cancer	2
Gynecological cancer	2
Gastric cancer	1
Colorectal cancer	1
Cholangiocellular cancer	1
Cancer, unknown primary	1
Melanoma	1
Cytologic type	
Adenocarcinoma	48
Squamous cell carcinoma	9
Small-cell carcinoma	2
Melanoma	1
Median number of organs involved (range)	4 (2–8)
Site of disease	
Mediastinal lymph node enlargement (subcarina)	48 (29)
Pleural effusion (bilateral)	40 (21)
Clinical manifestation at presentation	
Dyspnea	52
Fatigue	50
Cough	21
Hypotension	16
Edema	4
Chest pain	3
Abnormal ECG (low voltage, or tachycardia)	19
Median interval between the visceral and parietal pericardium (range)	
Echocardiography	22 mm (12–48)
Computed tomography	15 mm (10–25)

colorectal cancer, cholangiocellular cancer, melanoma, and primary unknown cancer in 1 patient each. About 14 patients had developed MPCE at the time of the diagnosis of their malignant disease, and all 14 of those patients were diagnosed with primary lung cancer. MPCE occurred in 7 patients as initial site of recurrence (5 patients with lung cancer, and 1 patient each with breast cancer and esophageal cancer), and the median interval until recurrence was 28.9 months (range 6.5–171 months). About 21 patients, including one patient treated with concurrent chemoradiation therapy had a prior history of chemotherapy. And 11 patients experienced disease progression in the form of MPCE during systemic chemotherapy, including during concurrent chemoradiation therapy in two patients. Seven patients developed MPCE during supportive care after their disease had recurred in other sites.

Around 50 patients underwent subxiphoid pericardiostomy, and percutaneous tube pericardiostomy was performed in the remaining 10 patients. No patients died as a direct result of either procedure. The median total volume of fluid drained was 953 ml (range 200–3970 ml). The median duration of drainage was 6 days (range, 1–33 days). There was no statistical difference in time to recurrence of MPCE or survival between patients undergoing tube pericardiostomy and subxiphoid pericardiostomy. ($P = 0.69$, $P = 0.42$, respectively) Among the 13 patients in whom sclerotherapy was performed, bleomycin was used as the agent in 10 patients, OK-432 in 2 patients, and minomycin in one patient. There was no statistical difference in time to recurrence of MPCE or survival in patients with or without sclerotherapy ($P = 0.71$, $P = 0.48$, respectively). Complications during pericardial drainage included atrial fibrillation in 5 patients, premature ventricular contractions in 3 patients, and chest pain in one patient.

MPCE recurred in 14 patients (6 with breast cancer, 6 with lung cancer, and one each with esophageal cancer and melanoma), including in 2 patients who underwent bleomycin sclerosis. The median interval until recurrence was 4.3 months (range 0.25–12 months), and pericardial drainage was performed in 9 of them (6 with breast cancer and 3 with lung cancer). Subxiphoid pericardiostomy was used again in 7 patients, and percutaneous tube pericardiostomy was used in the other 2 patients. Only one patient developed a second recurrence 7 weeks after removing the tube, and subxiphoid pericardiostomy was used to treat it. The median overall survival was 6.1 months, and the 1-year survival rate was 28% (range 0.25–48.4 months Fig. 1). The hospital mortality rate was 12% (7 of 60 patients), and the primary cause of death was the underlying malignancy in 6 patients and atrial perforation during subxiphoid pericardiostomy for recurrence of MPCE.

Table 2 shows the results of the univariate analysis for a relationship between the pretreatment variables, recurrence of the MPCE, and overall survival. There was no predictive factor for recurrence of MPCE. The Multivariate analysis yielded the following prognostic factors: performance status (hazard ratio, 2.1; 95%CI, 1.1 to 4.2; $P = 0.03$), occurrence of MPCE during chemotherapy (hazard ratio, 2.3; 95%CI, 1.1–4.7; $P = 0.02$), mediastinal lymph node enlargement (hazard ratio, 3.3; 95%CI, 1.3–8.1; $P = 0.011$), and cytologic type (hazard ratio, 3.1; 95%CI, 1.5–6.3; $P = 0.001$).

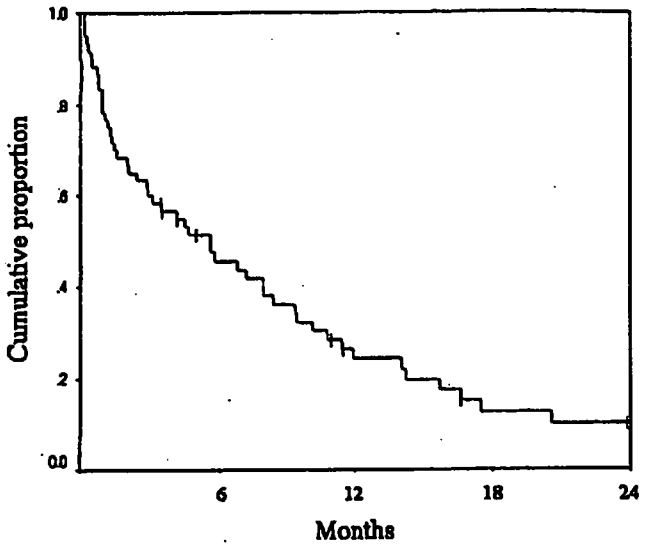

Fig. 1 Kaplan–Meier analysis of overall survival

Discussion

In the present study, we retrospectively analyzed cytology-positive MPCE cases, and the median survival time tended to be longer than in the previous studies. The prognostic value of pericardial fluid cytology was a matter of controversy in previous studies [8, 9, 12]. Since pericardial effusion is frequently caused by a cytopathology-negative cancer-related etiology, such as post-radiation therapy, post-bone marrow transplantation, and post-thoracic surgery [6, 12], the diagnosis based on cytopathologic confirmation is important in survival and prognostic analysis.

The pathways to the pericardium is considered: lymphatic, hematogeneous metastasis, direct tumor invasion, and retrograde lymphatic migration of tumor cells which involves mediastinal lymph nodes [13, 14]. Although it is difficult to distinguish direct invasion from retrograde lymphatic migration on CT scan images, the mediastinal lymph nodes, including the subcarina lymph node, were most common site of metastasis in this study. The presence of mediastinal lymph node enlargement was identified as a poor prognostic factor, and it may have contributed to obstruction of lymphatic drainage and retrograde tumor spread.

MPCE is uncommon in the absence of any other metastatic disease or as the primary manifestation of malignancy [2, 15, 16]. One fifth of the patients in our study had MPCE as the primary manifestation of malignancy, and all of them were diagnosed with primary lung cancer. The variables such as MPCE at the time of initial diagnosis or initial recurrence caused by MPCE, were not poor prognostic factors, patients with these rare manifestations have indications for systemic anticancer therapy for their cancer after the MPCE drainage procedures. On the other hand, MPCE during chemotherapy was found to be a poor prognostic factor in this study. This factor means MPCE developed with chemotherapy-resistant condition and it may be essentially severe visceral crisis, even if cardiac tamponade was rescued by drainage.

The efficacy of systemic anticancer therapy in controlling MPCE after the initial therapeutic pericardiocentesis, was 67.4% in the previous report (71.1% in breast cancer, 33.3% in other solid tumors, 100% in lymphomas) [16]. Performance status thought to be generally related with survival in patients treated with chemotherapy and present study indicated poor performance status was one of prognostic factors. Therefore, patients with favorable performance status may have a chance to achieve good condition with longer survival by receiving anticancer therapy after pericardial drainage.

Symptomatic MPCE can be effectively relieved by several procedures, but they need to be individualized based on consideration of both the underlying malignant disease and medical status of patient. Simple pericardiocentesis may be life-saving in emergency cases of cardiac tamponade. Although medical, interventional, or surgical treatment is recommended in almost all patients because of the high rate of recurrence, whether partial pericardiectomy, subxiphoid pericardiostomy, percutaneous balloon tube pericardiostomy, percutaneous tube pericardiostomy with or without sclerotherapy, radiotherapy, or systemic chemotherapy is the optimal method of management of MPCE has been a matter of controversy [17].

Several investigators retrospectively compared procedures [12, 18, 19]. Due to their short-life span, McDonald et al. [18] recommended percutaneous tube pericadiostomy for MPCE patients with positive-cytology. Although one patient in our study died, because of atrial perforation during subxiphoid pericardiostomy for MPCE recurrence, subxiphoid pericardiostomy was considered to have-high success rate with an acceptable risk [6, 9–11, 20].

Although the present study showed no statistical difference for clinical outcome in patient with or without sclerotherapy, the efficacy of sclerotherapy is unknown in patient with MPCE [21]. To obtain clear evidence of the effectiveness of sclerotherapy for the management of MPCE, we joined Japan Clinical Oncology Group (JCOG) 9812 trial, a randomized trial comparing instillation of bleomycin with no instillation of a sclerosing agent, and we hope that the results of the JCOG 9812 trial will be conclusive.

Conclusions

Pericardial drainage should be performed for immediate symptom relief in patients with MPCE, and it makes it

Table 2 Univariate analysis of pre-treatment variables.for recurrence of MPCE and overall survival

Variables	No. of pts	No. of MPCE recurrence	*P* value*	Median survival time (months)	*P* value**
Gender					
Male	30	6	0.54	3.4	<0.01
Female	30	8		12.5	
Age (years)					
60 ≤	28	7	0.78	6.1	0.9
60>	32	7		4.9	
Disease					
Lung cancer	34	6	0.23	5.1	0.68
Other	26	8		6.1	
Cytologic type					
Adenocaricinoma	48	10	0.45	7.9	<0.01
Other	12	4		1.25	
Performance status					
3 ≤	15	3	0.99	1.4	0.21
3>	45	11		5.9	
No. of metastatic site					
≤	23	4	0.53	3.2	0.44
4>	37	10		8.6	
Mediastinal lymph node enlargement					
Present	48	10	0.45	3.4	<0.01
Absent	12	4		22.4	
Pleural effusion					
Present	40	9	0.99	4.2	0.06
Absent	20	5		8.1	
MPCE at the time of diagnosis					
Present	14	3	0.99	4.2	0.75
Absent	46	11		5.7	
MPCE was initial site of recurrence					
Yes	7	1	0.99	13	0.11
No	53	13		4.5	
MPCE occurred during chemotherapy					
Yes	11	1	0.43	1.3	<0.01
No	49	13		7.0	
Prior history of chemotherapy					
Yes	21	6	0.58	5.9	0.34
No	39	8		4.2	

* Statistical analyses was performed by Pearson chi-square test/Fisher exact test

** Statistical analysis was performed by log-rank test

possible to prolong survival by preventing sudden life-threatening hemodynamic failure. Patients without poor prognostic factors may be recommended to consider further indications for systemic anticancer therapy.

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Original Article

The Q-Q Plot of p-values for Predicting Outcomes with the Gene Expression Data

Yoichi M. Ito*1, Yasuhiro Fujiwara*2 and Yasuo Ohashi*1

*1Department of Biostatistics/Epidemiology and Preventive Health Sciences, School of Health Sciences and Nursing, University of Tokyo
*2Breast and Medical Oncology Division, Department of Medical Oncology, National Cancer Center Hospital
ito@epistat.m.u-tokyo.ac.jp

Michiels et al. (2005) showed that a list of genes identified as predictors of prognosis via a non-repeated training – validation approach is unstable and advocate the validation by repeated random sampling. They considered that the genes which were selected as top 50 genes in more than half of their jackknife samples were stable for prediction. However, there is no rationale of the determination of the length of the gene list and the threshold of stability. Since evaluating an accumulation of low p-values in the repeated random sampling is essentially required for a stability assessment, it is better to compare the distribution of p-values of a gene observed with the distribution of p-values under the null hypothesis directly. In this study, the Quantile-Quantile plot (Q-Q plot) of p-values with null reference was proposed for this purpose. We applied the proposed method to a clinical data for primary breast cancer. The Q-Q plot approach can reveal that the genes with a similar p-value in the ordinary analysis have different p-value distributions in the repeated random sampling, and the gene with low p-values accumulated in the repeated random sampling could be evaluated according to the reference lines in the Q-Q plot.

Key words: bootstrap sampling, gene expression analysis, validation, Q-Q plots.

1. Introduction

Recently, cDNA microarray technology development produces an enormous amount of gene expression data. DNA microarrays are assays for quantifying the types and amounts of mRNA transcripts present in a collection of cells. The number of mRNA molecules derived from transcription of a given gene is an approximate estimate of the level of expression of that gene. In the proof of concept study, it is important to explore relationship between gene expressions in cancer cells and clinical response to the drug, because it reveals signal pathways affected by the drug in cancer cells.

When we construct the model for predicting clinical response, selection of the important

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genes for inclusion in the model must be needed because the sample size is usually limited in contrast to the huge number of genes. This is called feature selection, which is a common first step when constructing the model for predicting clinical response based on microarray data (Simon et al., 2003). It is generally reasonable to assume that only some subset from many measured genes contribute useful information for prediction. An approach to feature selection, therefore, is to select genes according to their statistical significance in the univariate regression analysis.

To estimate the accuracy of a feature selection based on the statistical significance, the standard strategy is via a training – validation approach, in which a training set is used to identify the candidate genes and a validation set is used to estimate the accuracy of prediction. Michiels et al. (2005) reanalyzed the data of published works about prediction of cancer outcome with microarrays by the delete-d jackknife sampling (Efron and Tibshirani, 1993). They revealed that the list of genes identified as predictors of prognosis was highly unstable; molecular signatures (based on one training set and the accuracy evaluated in one validation set) strongly depended on the selection of patients in the training sets. Therefore they advocate the use of validation by repeated random sampling.

Their validation approach was described as follows. First, the dataset (size N) with a binary outcome (dead or alive) was divided using the delete-d jackknife sampling into 500 training sets (size n) with $n/2$ patients having each outcome, and 500 associated validation sets (size $N-n$). Second, they identified a molecular signature for each training set and estimated the proportion of misclassifications for each associated validation sets. For a given training set, the molecular signature was identified as the 50 genes for which expression was most highly correlated with prognosis as shown by Pearson's correlation coefficient. They saw that the list of 50 genes that had the highest correlations with outcome was very unstable. For instance, with data by van't Veer and colleagues (van't Veer et al., 2002) and a training set of the same size as in original publication ($n = 78$), only 14 of 70 genes from the published signature were included in more than half of their 500 signatures. Also, ten genes not included in more than 250 of their signature.

They considered that the genes which were selected as top 50 genes in more than half of their jackknife samples were stable for prediction. However, there is no rationale of the determination of the length of the gene list and the threshold of stability. Since evaluating an accumulation of low p-values in the repeated random sampling is essentially required for a stability assessment, it is better to compare the distribution of p-values of a gene observed with the distribution of p-values under the null hypothesis directly.

The Q-Q plot is one of the useful methods for comparing the observed distribution of p-values to the null distribution. Wartenberg and Northridge (1991) proposed a method with the Q-Q plot to describe and summarize case-control data for exploratory analyses of disease-exposure relations. Holmgren (1995) discussed the properties of the probability-probability plot and the Q-Q plot as a description of treatment effect in a randomized controlled trials. Ito and Ohashi

(2001) proposed the theoretical Q-Q plot of the observed distribution of p-values for exploring the association between the gene expression and the pharmacokinetic parameter (Cmax) in the proof of concept study. Their theoretical Q-Q plot was, however, assumed the independence of p-values, observed p-values of regression with same Cmax variable are correlated with each other. Theoretical distribution based on the assumption of independence of the tests is inappropriate for the reference distribution of the observed distribution of p-values. In this study, we propose the visualization method of p-value distribution with the reference lines based on the normal random numbers, and apply to prediction of the clinical response with gene expression in cancer cell. In the next section, we present the proposed method. In Section 3, we describe the background of applied clinical data, and the proposed method is applied to the data. Finally, Section 4 provides some discussion.

2. The Q-Q plot of p-values with null reference

Wilk and Gnanadesikan (1968) proposed the empirical Q-Q plot for comparison of two one-dimensional samples. This is the useful method for visualizing the discrepancy of the observed distribution from the theoretical distribution. It is also useful for visualization of p-value distributions in the cross validation data sets.

Figure 1 is a diagram of the bootstrap sampling algorithm for Q-Q plot of p-values with null reference. First, we assumed that there is a dataset of size n which include one clinical response and g gene expressions. And the m sets of independent normal random numbers with size n are generated and merged to the original dataset. Second, b bootstrap samples are sampled from the merged dataset, and we consider the following model for the response:

$$g[E(y_i)] = \beta_{0j} + \beta_{1j} x_{ij}, \qquad i = 1,\ldots,n, \quad j = 1,\ldots,g, \tag{1}$$

where x_{ij} is the jth gene expression of ith subject, β_{0j} and β_{1j} are the intercept and slope parameter for jth gene respectively, and the function $g[\,]$ is the link function between the expectation of the response $E(y_i)$ and the linear predictor with the gene expression x_{ij}. The model (1) is applied to the b bootstrap samples, and b p-values for each of g genes about the slope parameter are estimated under the null hypothesis $\beta_{1j} = 0$. Third, we consider the following model for m sets of normal random numbers:

$$g[E(y_i)] = \gamma_{0k} + \gamma_{1k} z_{ik}, \qquad i = 1,\ldots,n, \quad k = 1,\ldots,m, \tag{2}$$

where $z_{ik} \sim N(0,\sigma^2)$, γ_{0k} and γ_{1k} are the intercept and slope parameter for kth random number respectively. The standard deviation of random numbers σ could be determined based on the distribution of gene expression in the applied data. The model (2) is applied to the b bootstrap samples, and b p-values for each of m sets of random numbers about the slope parameter are estimated under the null hypothesis $\gamma_{1k} = 0$. Even though two sets of random numbers are

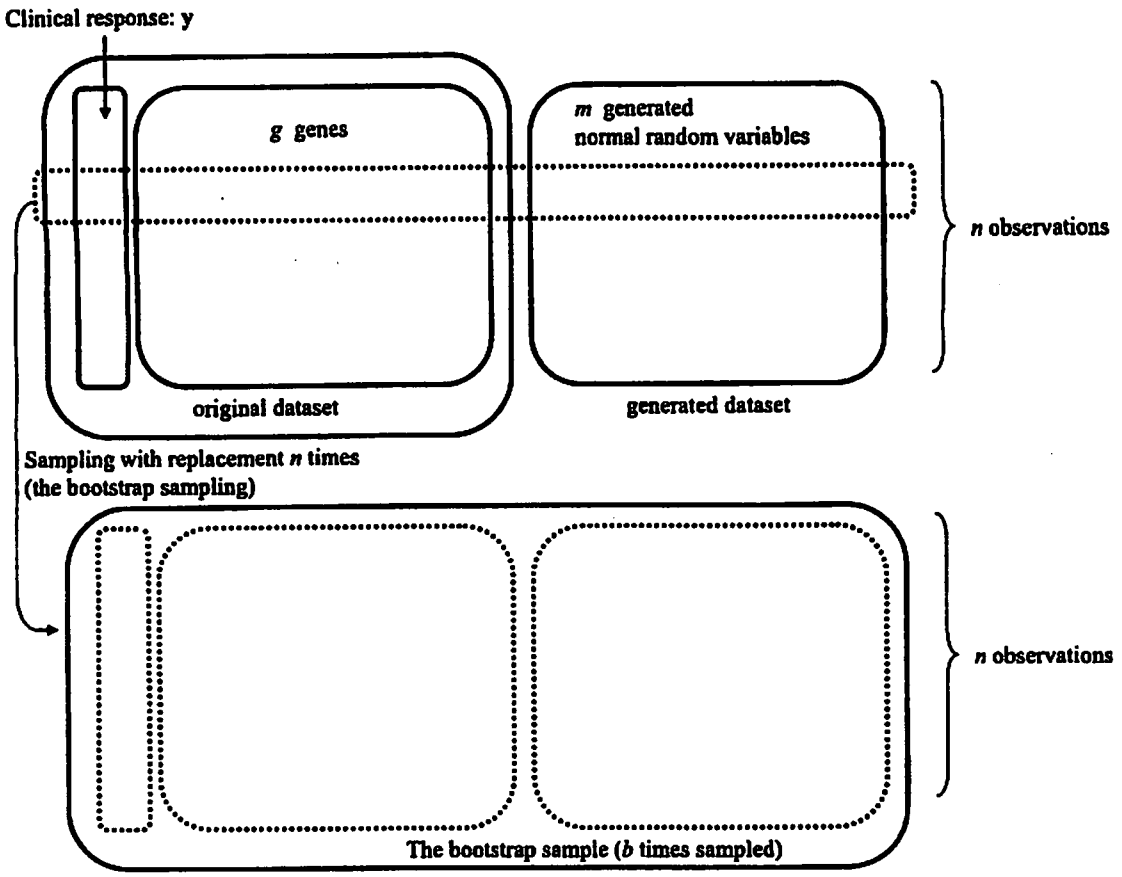

Fig. 1. The diagram of the bootstrap sampling algorithm for the Q-Q plot of p-values with null reference.

generated independently, calculated p-values for prediction are correlated among the bootstrap samples because the same outcome variable is predicted. To accommodate the correlation of p-values, m sets of random numbers must be fixed before the bootstrap sampling. Finally, we obtain g empirical distributions of p-values for the gene of size b and m empirical distributions of p-values for random numbers of size b. The negative logarithms of p-values are calculated for stressing on the region of low p-values.

When we sort the negative logarithms of p-values for each m sets of random numbers descendingly, we can obtain rth $(r = 1, \ldots, b)$ order statistic. There are m replicates of rth $(r = 1, \ldots, b)$ order statistic, then we can consider p percentile of rth $(r = 1, \ldots, b)$ order statistic. We plot p percentile of rth order statistic on y-axis and the median of rth order statistic on x-axis, and join these points. This Q-Q plot is called the p percentile of null reference in our approach.

Similarly, the negative logarithms of p-values for a gene are sorted in descending order, we can obtain rth $(r = 1, \ldots, b)$ order statistic for the gene. We plot the rth $(r = 1, \ldots, b)$ order statistic for the gene on y-axis and the median of rth $(r = 1, \ldots, b)$ order statistic for random numbers on x-axis. Comparing the Q-Q plot for the gene with each p percentile of null reference,

we can know whether the p-values of the gene are smaller than the expected values under the null hypothesis.

If the Q-Q plot is near to the upper left corner of the plot, there are more lower p-values than expected. Therefore we consider the area under the curve (AUC) as the index of the discrepancy from the null distribution. AUC is calculated by the trapezoidal method. If the AUC of a gene is larger than the AUC of 95th percentile of null reference, then the probability of obtaining such a large AUC can be found less than 5% under the null hypothesis.

The value of m and the bootstrap sample size b are tuning parameters for Q-Q plots. Large values of m produce more precise estimates of the p percentile of null reference and large values of b produce smoother Q-Q plots, but this further increases the computational burden because p-values must be calculated $b \times m$ times for the null reference and $b \times g$ times for the Q-Q plots for the genes. To assess the precision of the p percentile of null reference, we consider the confidence interval of p percentile (Altman et al., 2000). For the p percentile, first calculate the following quantities:

$$l_p = mq - Z_{1-\alpha/2} \times \sqrt{mq(1-q)} \quad \text{and} \quad u_p = 1 + mq + Z_{1-\alpha/2} \times \sqrt{mq(1-q)} \tag{3}$$

where $q = p/100$ and $Z_{1-\alpha/2}$ is the $100(1-\alpha/2)$ percentile of the standard normal distribution. Then round l_p and u_p to the nearest integers. The l_pth and u_pth observations in the sorted m replicates of rth $(r = 1, \ldots, b)$ order statistic are the $100(1-\alpha)\%$ confidence limits for the p percentile of the null reference. It is preferable that the confidence interval of a percentile dose not include the confidence limit of the adjacent percentile and the boundary of the observation list (1st and mth observations). For example, if we consider the 95% confidence interval of the 99th and 95th percentiles of null reference, then $l_{99} > u_{95}$ and $u_{99} \leq m$ are required. These yield $m \geq 298$ and $m \geq 476$ respectively. In practice, the value of m should be larger than these figures.

3. Applied Example

We applied the proposed method to phase II study data of neoadjvant 5FU/epirubicin/cyclophosphamide followed by weekly paclitaxel for primary breast cancer (Shimizu et al., 2005). The number of patients who is evaluated about pathological response and gene expression in both cancer cells and normal peripheral mononuclear cells are 34. The frequency of pathological response was as follows; grade 1a or 1b was 20, grade 2 was 5 and grade 3 was 9. Gene expression was measured by Custom ATLAS^{TM}Array (BD Biosciences Clontech) which can measure 988 genes at once.

We construct a prediction model for pathological response with gene expressions. Because pathological response is ordinal, we consider the following proportional odds model:

$$\log \frac{\pi_c}{1-\pi_c} = \beta_{0cj} + \beta_{1j} x_{ij}, \qquad i = 1, \ldots, 34, \quad j = 1, \ldots, 988, \quad c = 1, 2, 3 \tag{4}$$

Table 1. The top 20 genes with the lowest p-values according to the proportional odds model in the original data.

No	Gene ID	Parameter Estimate	Standard Error	Wald Chi Square	Wald p-value	Likelihood Ratio Chi Square	Likelihood Ratio p-value
1	Gene949	1.98	0.78	6.41	0.011	7.52	0.006
2	Gene218	2.63	1.16	5.16	0.023	5.99	0.014
3	Gene416	1.88	0.88	4.53	0.033	5.79	0.016
4	Gene26	1.57	0.68	5.33	0.021	5.67	0.017
5	Gene900	0.87	0.40	4.73	0.030	5.42	0.020
6	Gene449	1.46	0.65	4.97	0.026	5.37	0.021
7	Gene38	1.99	0.92	4.72	0.030	5.32	0.021
8	Gene592	1.19	0.59	4.01	0.045	4.78	0.029
9	Gene55	1.18	0.58	4.10	0.043	4.75	0.029
10	Gene437	1.63	0.81	3.99	0.046	4.72	0.030
11	Gene965	1.79	0.93	3.72	0.054	4.14	0.042
12	Gene782	-0.35	0.19	3.35	0.067	3.79	0.052
13	Gene75	1.18	0.63	3.51	0.061	3.76	0.053
14	Gene799	0.81	0.45	3.23	0.072	3.61	0.057
15	Gene860	1.78	0.97	3.35	0.067	3.46	0.063
16	Gene418	0.99	0.57	2.97	0.085	3.45	0.063
17	Gene859	0.67	0.39	2.84	0.092	3.44	0.064
18	Gene749	1.19	0.70	2.88	0.090	3.29	0.070
19	Gene883	0.58	0.38	2.32	0.128	3.28	0.070
20	Gene750	1.35	0.77	3.12	0.077	3.27	0.070

where $\pi_C = P(Y \leq c \mid x_{ij})$, c is the grade category of pathological response ($c = 1$ for grade 1a or 1b, 2 for grade 2 and 3 for grade 3).

Table 1 shows the top 20 genes with the lowest p-values according to the proportional odds model in the original data. The likelihood ratio p-values of 11 genes are less than 5%. Estimated odds ratio indicates a possibility of prediction for clinical response.

Figure 2 shows the null references and Q-Q plots of p-values of m sets of normal random numbers. The standard deviation of normal random numbers was determined at 0.3 based on the distribution of gene expression in the applied data. The value of m and the number of bootstrap sample b were both set at 1000. In Figure 2(a), the horizontal axis represents the median of rth ($r = 1, \ldots, b$) order statistic. The broken Q-Q plots represent the 1st, 5th, 10th, 25th, 50th, 75th, 90th, 95th, and 99th percentile of null reference and the values in parenthesis besides each curves are its AUC. When we consider Q-Q plots of each m sets of normal random numbers, we can obtain m Q-Q plots and AUCs. In Figure 2(b), the solid Q-Q plots represent Q-Q plots for the m sets of normal random numbers with corresponding percentile according to the AUC values. The AUC is given in parenthesis besides each curves. This figure shows the solid lines almost follow the broken lines, this implies the AUC is appropriate for the index of the discrepancy from the null distribution.

Figure 3 shows Q-Q plots of p-values with null reference for the top 3 genes according to the AUC values. The horizontal line in each Q-Q plot indicates the p-value in the original data. Left Q-Q plot with the highest AUC passes along between the 99th percentile and the 95th percentile of null reference, and then passes above the 99th percentile of null reference. This implies that

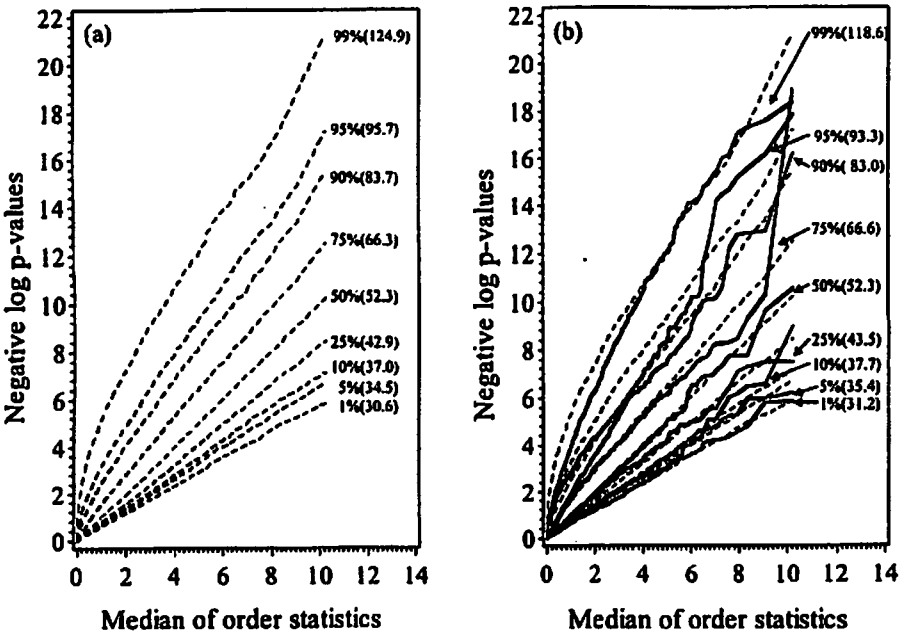

Fig. 2. The null references and Q-Q plots of p-values of m sets of normal random numbers. The values besides each curves indicate the corresponding percentile and AUC of the Q-Q plot in parenthesis.

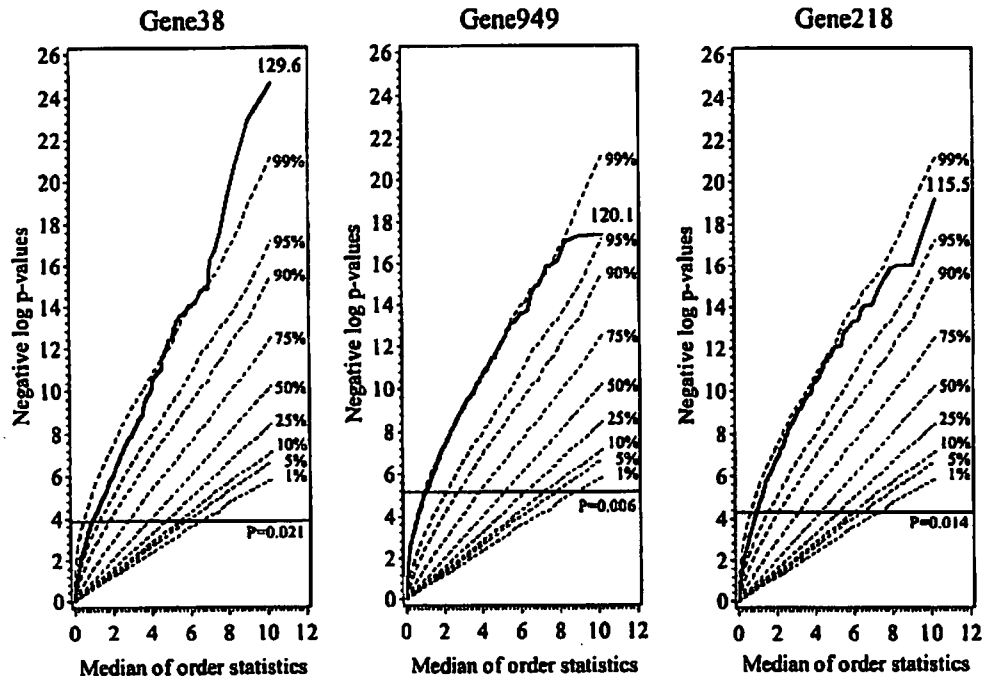

Fig. 3. The Q-Q plots of p-values with null reference for the top 3 genes according to the AUC. The horizontal line indicates the p-value in the original data. Dotted lines indicate the null references as shown in Figure 2(a).

the probability of obtaining the accumulation of low p-values is approximately less than 5% under the null hypothesis and there are some highly extreme low p-values. Although AUC of central Q-Q plot is smaller than AUC of left Q-Q plot, central Q-Q plot would be regarded as

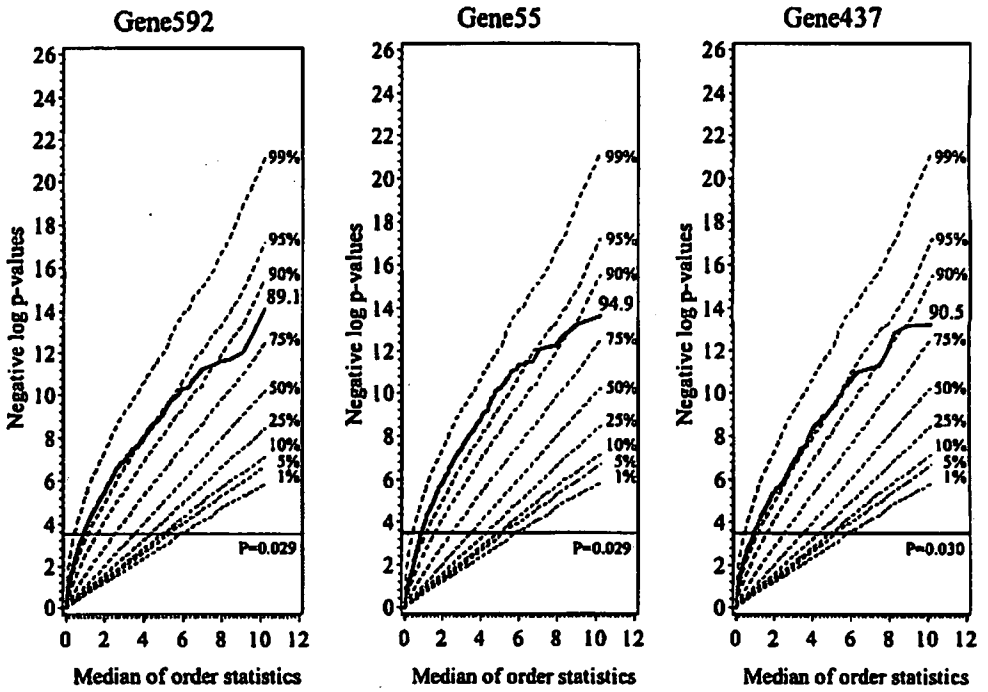

Fig. 4. The Q-Q plots of p-values with null reference of the genes whose p-value is around 3% in the original data. The horizontal line indicates the p-value in the original data. Dotted lines indicate the null references as shown in Figure 2(a).

more stable and significant than left Q-Q plot because central Q-Q plot almost follows the 99th percentile of null reference in the plot area where median of order statistic is less than 6. In fact, there are 98.6% of points for the Q-Q plot in this area. Thus we should pay attention to the shape of the Q-Q plot in this area.

Figure 4 shows the Q-Q plots of p-values with null reference of the genes whose p-value is around 3% in the original data. The curve of Gene55 almost lies between 99th percentile and 95th percentile of the null reference. On the other hand, the Q-Q plots for Gene592 and Gene437 follow the 95th percentile of the null reference. This imply that the Q-Q plot for Gene55 is more stable and significant than the other two Q-Q plots. Thus we could select Gene55 for the candidate gene.

4. Discussion

The Q-Q plot approach has an advantage for visualizing the whole distribution of the bootstrap p-values. As shown in the Figure 4, although the genes have a similar p-value in the ordinary analysis, their Q-Q plots make a difference. In addition, according to our approach, since there are the reference lines, we can evaluate the possibility that we obtain such a plot under the null hypothesis. If Q-Q plot of the gene observed lied above the 95th percentile of null reference, the probability of obtaining the bootstrap p-values was considered less than 5% under the null hypothesis.

The final objective of the study with microarray is the screening of the affected gene. After selecting the candidate genes, the confirmation experiments will be conducted about that genes. Therefore an important role of the analysis with microarray data is providing the more information for selecting the candidate genes. Our approach provides such information about the stability of the analysis. Since our approach is only the visualizing procedure of the p-value distribution, it can be applied not only to the class prediction study but also to the class comparison study (Simon et al., 2003).

Our approach is also useful for feature selection. In feature selection, we recommend the following approach. First draw some Q-Q plots with high AUC as shown in Figure 3. Then examine the shape of these Q-Q plots. If the Q-Q plot for a gene is near to the upper left corner of the plot and above a percentile (e.g. 99th percentile) of null reference, the gene would be regarded as stable and significant. Finally select such a gene for subsequent analysis.

While AUC may be sensitive to the extreme low p-values as shown in Figure 3 and may not be the most appropriate index of discrepancy from the null hypothesis, these would not cause a severe practical problem. Because our approach is not intended to compare AUC between two Q-Q plots, but to compare the shape of the Q-Q plot for a gene with a percentile of the null reference. In microarray experiments, we have to examine a huge number of genes. The AUC could be used as a rough guide in selecting the candidate genes for examination.

Our approach is very time-consuming since p-values for m sets of random numbers are calculated in each bootstrap process. To derive the theoretical reference lines accommodating the correlation of p-values would drastically reduce the computation time. This is an open question.

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Bladder Cancer

Weekly Paclitaxel and Carboplatin against Advanced Transitional Cell Cancer after Failure of a Platinum-Based Regimen

Tsutomu Kouno [a,*], *Masashi Ando* [a], *Kan Yonemori* [a], *Koji Matsumoto* [a], *Chikako Shimizu* [a], *Noriyuki Katsumata* [a], *Motokiyo Komiyama* [b], *Eijiro Okajima* [b], *Naoki Matsuoka* [b], *Hiroyuki Fujimoto* [b], *Yasuhiro Fujiwara* [a]

[a] *Medical Oncology Division, National Cancer Center Hospital, Tokyo, Japan*
[b] *Urology Division, National Cancer Center Hospital, Tokyo, Japan*

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Abstract

Objective: Weekly administration of paclitaxel plus carboplatin is hypothesized to be an effective second-line treatment for advanced transitional cell cancer after failure of platinum-based regimen. In this phase 2 trial, we tested this hypothesis.

Patients and methods: Patients with advanced transitional cell cancer who showed evidence of progressive or recurrent disease after methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) therapy were eligible for this study. Weekly paclitaxel (80 mg/m^2) and carboplatin (AUC 2) were administered on days 1, 8, 15, 22, 29, and 36; the cycle was repeated every 7 wk until disease progression or intolerable toxicity (maximum 18 doses).

Results: Thirty-five patients entered this study. Among the 31 patients who were assessable, 10 had an objective response (overall response rate: 32.3%, 95% confidence interval, 15.8–48.7%). The median progression-free survival (PFS) and median survival times were 3.7 and 7.9 mo, respectively. Among the 22 patients who received prior MVAC therapy for metastatic disease, 36% had an objective response; their median PFS and median survival times were 4.3 and 7.9 mo, respectively; neither survival time significantly differed from the survival time of those who received prior MVAC as adjuvant setting. Toxicities were mild except one toxic death due to neutropenic sepsis.

Conclusions: Weekly paclitaxel plus carboplatin was a manageable, active second-line treatment for advanced transitional cell cancer after failure of platinum-based therapy.

* Corresponding author. Medical Oncology Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. Tel. +81 3 3542 2511; Fax: +81 3 3542 3815.
E-mail address: tkouno@ncc.go.jp (T. Kouno).

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1. Introduction

Cisplatin-based regimens such as the combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC), and the combination of gemcitabine and cisplatin (GC) are considered standard treatment for advanced urothelial cancer [1,2], but there is no standard treatment for patients who fail such a cisplatin-based regimen. Among newer active agents for urothelial cancer, paclitaxel yielded a 42% response rate as first-line therapy [3]. However, against previously treated patients, the response rate was only 10% [4].

Because platinum is the most active agent for urothelial cancer, salvage therapy for advanced urothelial cancer often includes a platinum agent as a component of combination chemotherapy regimens, such as paclitaxel, methotrexate, and cisplatin [5] or gemcitabine, ifosfamide, and cisplatin [6]. These regimens are active not only against platinum-sensitive disease but platinum-resistant disease. Although these combinations yielded a higher response rate, the toxicities they induced were severe, especially in previously treated patients.

Carboplatin is a less nephrotoxic and less emetogenic platinum compound in which a cyclobutanedicarboxylate moiety has been substituted for the two chloride ligands of cisplatin, and it is more suitable for use in renal-impaired or heavily treated patients. Against urothelial cancer, carboplatin has shown modest activity (14% response rate) [7], but whether carboplatin is inferior to cisplatin is unclear, especially when combined with paclitaxel [8,9]. The combination of paclitaxel and carboplatin is a widely used and effective regimen for ovarian cancer and non–small-cell lung cancer. In a phase 3 randomized controlled trial of first-line therapy for advanced urothelial cancer, the patients who received paclitaxel plus carboplatin had a median survival of 13.8 mo, which was similar to the 15.4 mo obtained with MVAC [9]. Although these results must be interpreted with caution because the study failed to reach its accrual goal, the combination of paclitaxel and carboplatin might have significant activity against urothelial cancer with less toxicity.

Carboplatin has been found to have a synergistic effect with paclitaxel on ovarian cancer in vitro [10]. This combination may have activity even in patients previously treated with platinum [10]. Furthermore, weekly administration of paclitaxel versus administration every 3 wk has been reported to have superior activity against metastatic breast cancer, with sustained cumulative exposure and dose-dense drug delivery [11]. Weekly paclitaxel plus carboplatin has been reported to have significant activity against recurrent ovarian cancer [12], advanced non–small-cell lung cancer [13], and advanced breast cancer [14].

Since weekly administration of 135 mg/m^2 of paclitaxel plus the area under the curve (AUC) 2 of carboplatin already has been reported to be intolerable for predominantly chemotherapy-naïve patients with advanced urothelial cancer [15], weekly administration of 80 mg/m^2 of paclitaxel was considered to be more fit for previously treated patients.

On the basis of these data, we designed a phase 2 study of weekly paclitaxel plus carboplatin in patients with advanced urothelial cancer, after failure of a platinum-based regimen.

2. Patients and methods

2.1. *Eligibility and exclusion criteria*

Patients had to be 18 yr of age or older and have histologically proven transitional cell cancer (bladder, renal pelvis, ureter, or urethra) that was not curable by surgery or radiation therapy. Bidimensionally measurable disease documented within 28 d prior to registration was required. Patients had to have progressive or recurrent disease after MVAC therapy. Patients who had undergone prior treatment with adjuvant or neoadjuvant MVAC therapy were also eligible. At least 3 wk had to have elapsed since the completion of preceding chemotherapy or radiotherapy. Patients who had been treated with any taxanes were ineligible. Although an Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) of 0 to 3 had been an eligibility requirement in the early stage of this trial, after the toxic death of one patient with a PS score of 3, we did not accrue patients with this PS score. Adequate organ function with a normal electrocardiogram, absolute granulocyte count of at least 1500/mm^3, platelet count of at least 100,000/mm^3, serum total bilirubin of no more than 1.5 mg/dl, serum transaminase activity of no more than 100 level IU/l, and creatinine level of no more than 2.0 mg/dl were required. Patients with known central nervous system metastasis, active infection, or inadequately controlled diabetes were excluded.

The protocol was approved by the institutional review board of the National Cancer Center Hospital, and all patients provided written informed consent before treatment.

2.2. *Treatment regimen*

Creatinine clearance was estimated by using the Cockcroft-Gault formula. Paclitaxel was administered on an outpatient basis at a dose of 80 mg/m^2 by 1-h infusion followed by carboplatin at AUC of 2 mg·min/ml by 1-h infusion. Dexamethasone 8 mg, ranitidine 50 mg, and chlorpheniramine 10 mg were administered prior to the paclitaxel infusion to prevent a hypersensitivity reaction. Granisetron 3 mg was administered prior to the carboplatin infusion. The paclitaxel followed by carboplatin was administered on days 1, 8, 15, 22, 29, 36, and repeated three times every 7 wk until disease