（資料）　分担研究者　大橋

図1. p値の負の対数の合計を指標とした場合の参照線

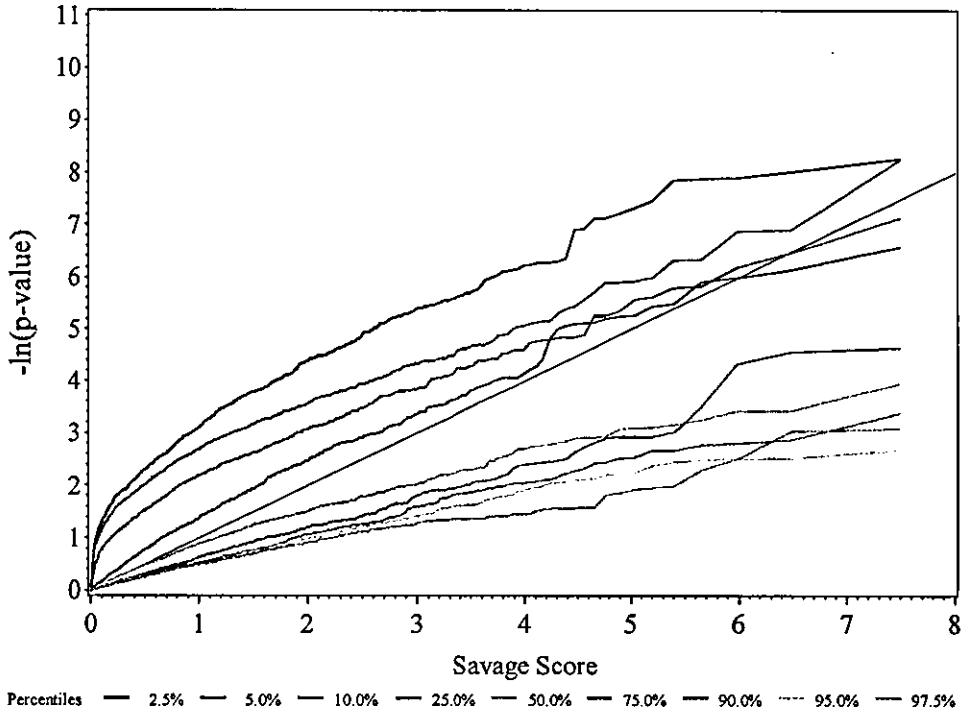

図2. プロットの曲線下面積を指標としたときの参照線

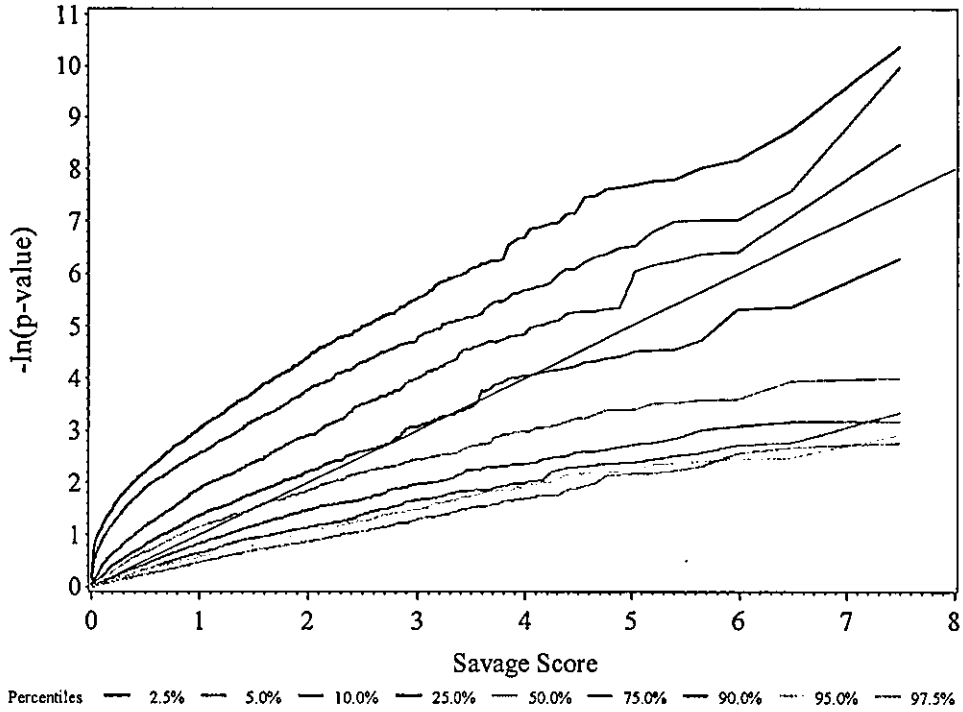

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表1. group 1および 2の遺伝子のAUCとオッズ比

group	GenBank Accession no.	AUC	Odds Ratios	2.5th Percentiles of Odds Ratio	97.5th Percentiles of Odds Ratio
1	Y00486	53.7	7.58	2.96	36.67
1	L19067	52.7	13.63	3.18	425.78
1	AF017786	49.0	6.99	1.83	88.34
1	AF011792	48.0	4.91	1.80	19.40
1	AF048700	46.8	3.29	1.28	15.85
1	X05030	46.2	0.71	0.32	0.92
2	M62402	43.7	6.60	2.50	38.65
2	X76220	43.5	2.44	1.44	4.79
2	U66879	42.7	0.22	0.01	0.83
2	M81934; S78187	42.7	4.36	1.85	14.37
2	U09178	40.0	3.38	1.55	10.60

＊AUC: Area Under the Curve

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図3. group 1の遺伝子のQ-Q plot

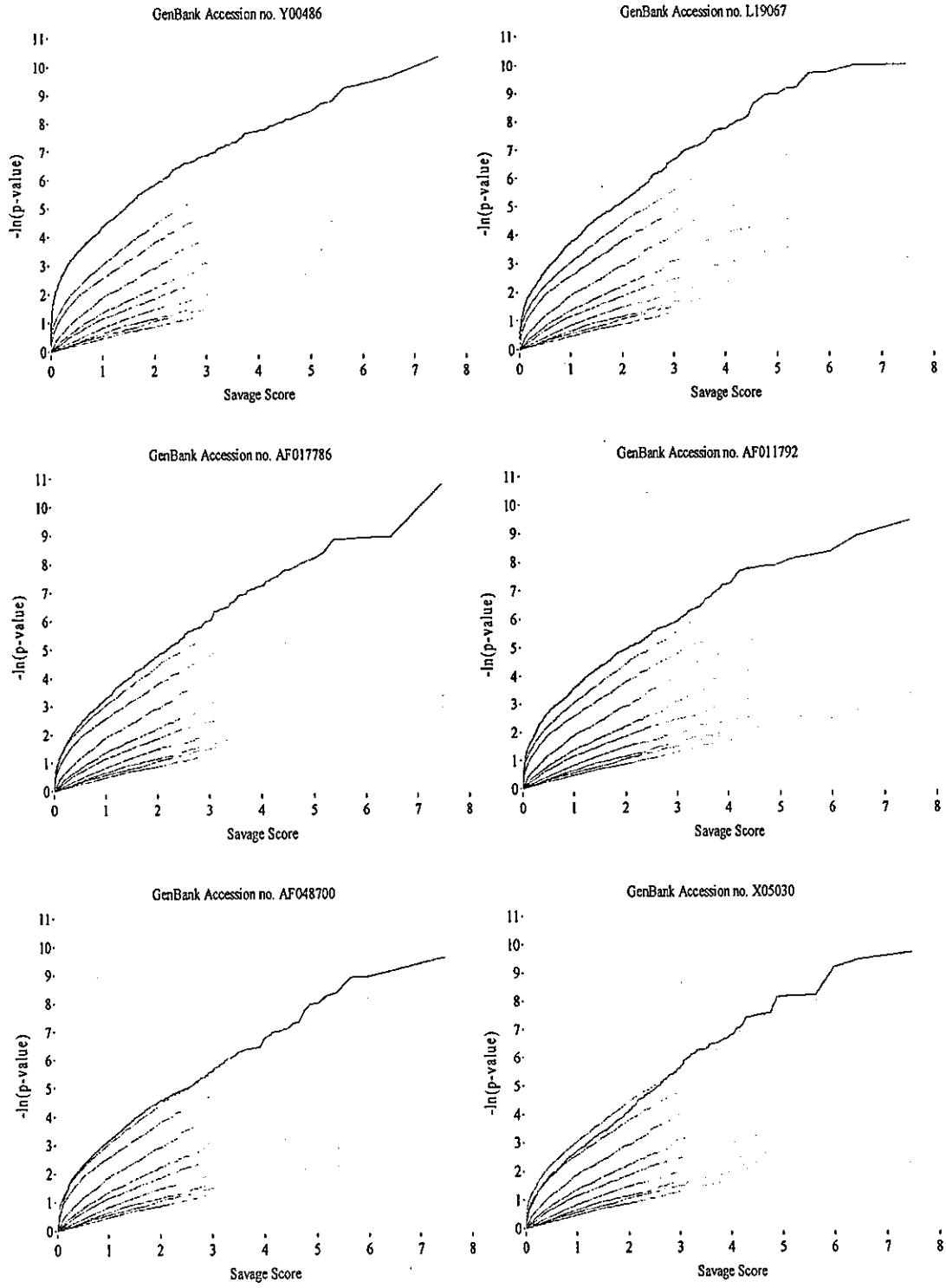

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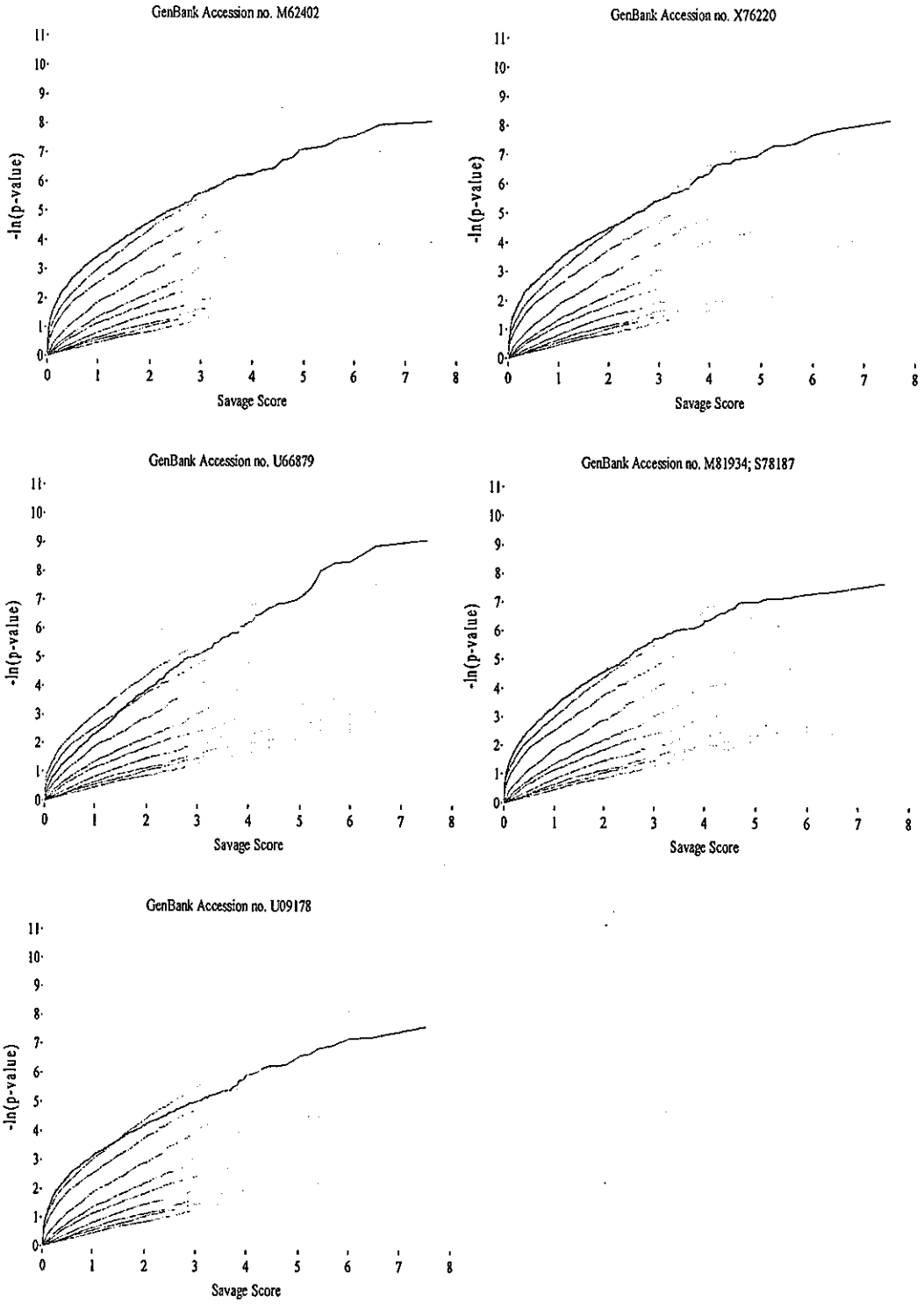
図4. group 2の遺伝子のQ-Q plot



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別添４

厚生労働科学研究費補助金（萌芽的先端医療技術推進研究推進事業）
分担研究報告書

Per Gene Basis Analysis による遺伝子発現の再現性に関する研究

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研究要旨　抗癌剤感受性遺伝子を検討する目的で，4 種類の乳癌細胞株，4 種類の接触処理の 16 通りの組み合わせについて，それぞれ 2 回の遺伝子発現量を測定している．本研究では、この実験データを用いて，遺伝子毎に遺伝子発現量の再現性を検討し，他の遺伝子に比べ，相対的に再現性の劣る遺伝子群を推定した．これらの遺伝子は乳癌細胞株あるいは接触処理の変化にともなう遺伝子発現解析の結果の解釈の際に注意を要する遺伝子である．

A．研究目的

マイクロアレイによる遺伝子発現データには，いろいろなばらつきの要因が存在するため，一般にその変動は大きく，測定データの信頼性評価は，遺伝子発現解析の結果の解釈上，重要な役割を占めると考えられる．前年度報告（フィルターアレイの信頼性および抗癌剤感受性遺伝子に関する研究）において，当該実験に用いたフィルターアレイの信頼性についてサンプル単位での検討を行った．すなわち，当該実験では，4 種類の乳癌細胞株，4 種類の接触処理の 16 通りの組み合わせについて，それぞれ 2 回の遺伝子発現変動を測定し，16 通りのサンプルのペアの相関係数を算出することで，その再現性を検討した．その結果，いずれのペアにおいても相関係数は一様に高値(0.8)を示した．

本研究では，サンプル単位での再現性の検討ではなく，さらに，遺伝子毎(Per Gene Basis)に再現性の検討を行い，発現量の安定していない遺伝子を探索する．乳癌細胞株あるいは接触処理間で変動の大きさの安定していない遺伝子については，乳癌細胞株あるいは接触処理の違いによる遺伝子発現量の変化に関する結果の解釈に注意を要する．

B．研究方法

1．実験方法

クロンテック社のアトラスフィルターアレイを用いて，4 種類の乳癌細胞株（BT474、MCF7、MDA-MB-231、SK-BR-3）についてそれぞれ，4 種類の接触処理（エストロゲンのみ、エストロゲンとタモキシフェン低用量、エストロゲンとタモキシフェン高用量、エストロゲンフリー）を行い，遺伝子発現量を測定した．16 通りの乳癌細胞株と接触処理の組み合わせに対し，それぞれ 2 回の繰り返しを行い，合計 32 枚のアレイからのサンプルを得た．各々のアレイにおいて， 825 種類の遺伝子

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に関する発現情報を測定した．なお，実験の順序に伴う系統的変動を除去するため，繰り返しをブロックとして，16 種類の組み合わせに対するハイブリダイゼーション処理の順番は無作為化を行い決定した。

2．解析方法

遺伝子データ解析パッケージ Bioconductor (*www.bioconductor.org*) に含まれる関数 VSN (Variance Stabilizing Transformation)を用いて，分散安定化変換をデータの前処理として行った（Huber (2002)）.

乳癌細胞株および接触処理の 16 種類の組み合せに対し，繰り返しによる変動を各遺伝子について以下の通り算出した.

分散安定化変換後の遺伝子 i $(i=1,\ldots,825)$ の発現量を y_{ijkl} とする。ここで j は乳癌細胞株 $(j=1,\ldots,4)$、k は接触処理 $(k=1,\ldots 4)$，l は繰り返し $(l=1,2)$ である．繰り返しに関する遺伝子発現量の差を $d(y_{ijk1},y_{ijk2})$ とし，遺伝子 i における発現量の差の中央値および分散

$$V_i=\sum_{j=1}^{4}\sum_{k=1}^{4}(d(y_{ijk1},y_{ijk2})-M_i)^2\Big/(16-1)$$

を求めた．ここで，M_i は，遺伝子発現量の差の算術平均

$$M_i=\sum_{j=1}^{4}\sum_{k=1}^{4}d(y_{ijk1},y_{ijk2})\Big/16,$$

である.

なお 発現量の差，$d(y_{ijk1},y_{ijk2})$ については，2 乗差 $d(y_{ijk1},y_{ijk2})=\left(y_{ijk1}-y_{ijk2}\right)^2$ を用いた.

C. 研究結果

2乗差の中央値の分布を図1に，また，2乗差の中央値が高値を示したものから順に 20 個の遺伝子を表1にリストした．図1のヒストグラムに示すとおり，ほぼ大部分の遺伝子について，2乗差の中央値は 4 以下であった．特に，RHO GDP-dissociation inihibitor 1 (RHO-GDI 1); RHO-GDI alpha (GDIA1); ARHGDIA については，他の値よりも1つだけ大きな値を示しており(7.924)，繰り返しによる再現性が他の遺伝子と比べ相対的に劣ることが示唆された.

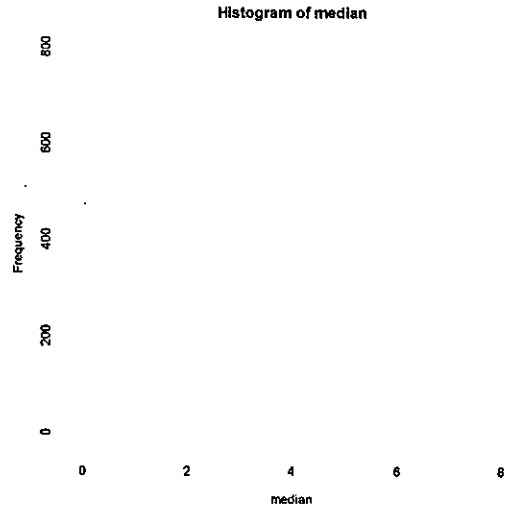

図1　2乗差の中央値のヒストグラム

2乗差の分散の分布を図2に，また，2乗差の分散が高値を示したものから順に 20 個の遺伝子を表2にリストした。図2に示すとおり，ほぼ大部分の遺伝子は 10 以下の値であった．RHO GDP-dissociation inihibitor 1 (RHO-GDI 1); RHO-GDI alpha

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(GDIA1); ARHGDI, tumor necrosis factor type 1 receptor-associated protein (TRAP1), および, Tyrosine-protein kinase receptor UFO precursor; axl oncogene については，2 乗差の分散が他の遺伝子よりも相対的に大きく（分散値はそれぞれ、18.25, 14.45, 13.69），乳癌細胞株間，接触処理間の違いにより，再現性が比較的変動しやすいことが示唆された．

これらの遺伝子については他の遺伝子に比べて、繰り返しによるバラツキが相対的に大きい，あるいは，再現性に関する乳癌細胞株間およびエストロゲン接触処理間でのバラツキが相対的に大きい遺伝子であるため、本実験から得られた遺伝子発現解析の解釈には注意を要する遺伝子である．

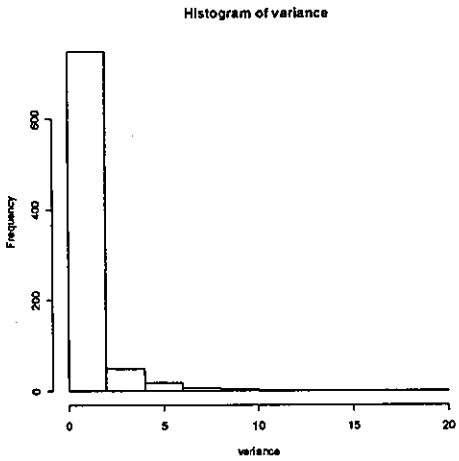

図２　　２乗差の分散のヒストグラム

D. 考察

乳癌細胞株あるいは接触処理の違いによる遺伝子発現強度の変化を検討するにあたり、同一細胞株、同一処理における遺伝子発現強度のバラツキが小さいこと，また，それらが同程度であることが望まれる。

本研究では，各遺伝子について、繰り返しによるバラツキの大きさ，接触要因あるは細胞株によらずそれらのバラツキの大きさが同程度であるかを検討した．その結果，いくつかの遺伝子について，他の遺伝子に比べて再現性の劣ることが示唆された．

なお，今回の実験では，乳癌細胞株を用いて検討を行っているため，実際に臨床検体を用いて検討を行った場合は，さらにバラツキは大きくなるものと考えられる。遺伝子発現データを収集するプロセス、すなわち、サンプルの採取から遺伝子発現強度の読み取りのまでの間には数々のバラツキの要因があるため、これらのバラツキの混入を小さくするような実験計画を立てることが重要である。また、同一条件で繰り返しを行なうことは、マイクロアレイによる研究における統計的推測に関する精度を向上するのみならず、今回行ったような、再現性の検討を可能とするので、計画上考慮すべき事項の１つであると言える。

E. 結論

今回の研究を行った結果、RHO GDP-dissociation inihibitor 1 (RHO-GDI 1); RHO-GDI alpha (GDIA1); ARHGDI など、いくつかの遺伝子について、他の遺伝子に比べ相対的に再現性の劣る遺伝子が推定された。

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F. 健康危険情報

該当なし.

G. 研究発表

該当なし.

H. 知的財産権の出願・登録情報

該当なし.

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（資料）　分担研究者　竹内

Gene Name	Coordinate	Median of Squared Difference
RHO GDP-dissociation inihibitor 1 (RHO-GDI 1); RHO-GDI alpha (GDIA1); ARHGDIA	C3e	7.924
cell division protein kinase 6 (CDK6); serine/threonine protein kinase PLSTIRE	A3k	4.831
Human paxillin mRNA, complete cds	F13d	4.590
neurotrophin 3 precursor (NT3); nerve growth factor 2 (NGF2)	A14l	4.444
rhoHP1	C3l	3.767
tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein epsilon polypeptide (YWHAE);14-3-3 protein epsilon; protein kinase C inhibitor protein 1 (KCIP1); mitochondrial import stimulation factor L subunit	C7g	3.477
c-myc proto-oncogene	A9m	2.994
casein kinase I alpha isoform (CKI-alpha); CK1; CSNK1A	C2f	2.949
cAMP-dependent protein kinase I alpha regulatory subunit (PRKAR1); tissue-specific extinguisher 1 (TSE1)	B9h	2.943
H1 histone family member 0 (H1F0; H10); H1FV	E11b	2.573
TSG101 tumor susceptibility protein	B11g	2.176
metastasis-associated protein 1 (MTA1)	B10n	2.037
Rho-related GTP-binding protein RhoE; Rho8; ARHE	C3f	1.982
cell cycle progression 2 protein (CPR2)	A4h	1.812
ERBB2 proto-oncogene; NEU proto-oncogene; HER2	B2h	1.770
interleukin 6 precursor (IL6); B-cell stimulatory factor 2 (BSF2); interferon beta 2 (IFNB2); hybridoma growth factor	D11e	1.690
growth factor receptor-bound protein 2 (GRB2); abundant SRC homology protein (ASH)	D7b	1.687
cyclin-dependent kinase 4 inhibitor 2D (CDKN2D); p19-INK4D	A8j	1.535
Homo sapiens pyruvate dehydrogenase kinase, isoenzyme 2 (PDK2), mRNA	F12g	1.417
retinoic acid receptor alpha 1 (RAR-alpha 1; RARA); PML-RAR protein	B8j	1.403

表１：2乗差の中央値の大きい遺伝子

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（資料）　分担研究者　竹内

Gene name	Coordinate	Variance of Squared Difference
RHO GDP-dissociation inihibitor 1 (RHO-GDI 1); RHO-GDI alpha (GDIA1); ARHGDIA	C3e	18.250
tumor necrosis factor type 1 receptor-associated protein (TRAP1)	D12b	14.453
Tyrosine-protein kinase receptor UFO precursor; axl oncogene	B11f	13.687
Homo sapiens v-akt murine thymoma viral oncogene homolog 3 (protein kinase B, gamma) (AKT3), mRNA	F12e	9.059
Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein epsilon polypeptide (YWHAE);14-3-3 protein epsilon; protein kinase C inhibitor protein 1 (KCIP1); mitochondrial import stimulation factor L subunit	C7g	8.892
neurotrophin 3 precursor (NT3); nerve growth factor 2 (NGF2)	A141	8.585
TIS11B protein; butyrate response factor 1 (BRF1); EGF response factor 1 (ERF1)	D9c	7.818
type II cytoskeletal 11 keratin (KRT11); cytokeratin 1 (CK1); 67-kDa cytokeratin; hair alpha protein	F8a	7.539
interleukin 1 alpha precursor (IL1-alpha; IL1A); hematopoietin 1	D10d	6.726
casein kinase I alpha isoform (CKI-alpha); CK1; CSNK1A	C2f	6.611
transforming growth factor beta 3 (TGF-beta3; TGFB3)	D8d	6.250
serine/threonine protein kinase SAK	B11n	6.082
68-kDa tumor protein (TP68); p51B	A6n	5.980
insulin-like growth factor-binding protein 2 (IGF-binding protein 2; IGFBP2; IBP2)	D7j	5.908
Homo sapiens cytochrome P450, subfamily IIIA (niphedipine oxidase), polypeptide 5 (CYP3A5), mRNA	F13f	5.640
Human paxillin mRNA, complete cds	F13d	5.460
ras-related C3 botulinum toxin substrate 2; p21-rac2; small G protein	B5m	5.459
farnesyl pyrophosphate synthetase (FPS); farnesyl diphosphate synthase (FDPS); dimethylallyltranstransferase; geranyltranstransferase; KIAA0032	C6i	5.314
type II cytoskeletal 2 epidermal keratin (KRT2E); cytokeratin 2E (CK2E)	F8b	5.199
integrin beta 7 precursor (ITGB7)	C9g	5.152

表２：２乗差の分散の大きい遺伝子

別添５

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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Efficacy of weekly paclitaxel in patients with docetaxel-resistant metastatic breast cancer

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Key words: docetaxel, metastatic breast cancer, paclitaxel, predictive factor, resistance, taxane

Summary

Background. Partial cross-resistance to paclitaxel and docetaxel has been demonstrated in pre-clinical studies.

Patients and methods. We retrospectively evaluated the efficacy of weekly paclitaxel 80 mg/m^2 in 82 patients with docetaxel-resisitant metastatic breast cancer. Docetaxel resistance was classified into primary resistance, defined as progressive disease while receiving docetaxel, and secondary resistance, defined as progression after achievement of a documented clinical response to docetaxel. Secondary resistance was subclassified according to the interval between the final infusion of docetaxel and the start of weekly paclitaxel into: (1) short interval, ≦120 days, and (2) long interval, >120 days.

Results. The response rate of the 82 patients was 19.5% (95% confidence interval, 10.8–27.9%). The response rate according to the docetaxel resistance category was: primary resistance ($n=24$), 8.3%; secondary resistance ($n=58$), 24.1% (short interval [$n=39$], 17.9%, and long interval, [$n=19$], 36.8%). The differences in response rates among the three categories were statistically significant ($p=0.0247$, Cochran–Mantel–Haenszel test). The interval between from the final docetaxel infusion and disease progression were predictors for response of weekly paclitaxel.

Conclusion. Weekly paclitaxel is modestly effective and safe in docetaxel-resistant metastatic breast cancer patients. However, weekly paclitaxel should not be recommended for primary resistance patients with docetaxel.

Abbreviations: MBC: metastatic breast cancer

Introduction

Paclitaxel and docetaxel are currently two of the most effective anticancer drugs in breast cancer chemotherapy [1, 2]. Paclitaxel and docetaxel are the first members of a class of microtubule-stabilizing anticancer agents. They bind to the β-tubulin subunit of the tubulin hetero-dimer, accelerate the polymerization of tubulin, and stabilize the resultant microtubules to inhibit their polymerization. This inhibition results in the arrest of the cell division cycle, mainly at the G2/M2 stage, which triggers the cell signaling cascade, leading to apoptosis of the cancer cells [3–6]. Although the mechanism of action of paclitaxel and docetaxel is similar, there are several notable differences in the way they form stable, non-functional microtubule bundles, and in the affinity of the two compounds

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for binding sites [7]. Pre-clinical studies have demonstrated docetaxel to be 100-fold more potent than paclitaxel in achieving bcl-2 phosphorylation and apoptotic cell death, and the cellular uptake of docetaxel is greater than that of paclitaxel, both of which lead to greater cytotoxic activity [8, 9]. *In vivo* evidence has suggested the existence of partial cross-resistance between the two drugs despite the fact they share a similar antitumor mechanism [10].

Paclitaxel and docetaxel have shown similar clinical efficacy in patients with anthracyline-resistant metastatic breast cancer (MBC) [1], and the response rate to both was almost the same: 21.5–53% to weekly paclitaxel, and 22.9–57% to docetaxel [10–16].

In retrospective study of Lin et al. observed a response rate of 25% in patients treated with docetaxel at a dose of 75 mg/m^2, who had pre-treated with anthracycline and paclitaxel [17]. In a phase II study Valero et al. observed a response rate of 18.1% in patients with paclitaxel-resistant MBC treated with deocetaxel at a dose of 100 mg/m^2 infused over 1 h every 3 weeks [18]. These studies suggested partial cross-resistance between paclitaxel and docetaxel [17, 18].

The taxanes, i.e., docetaxel and paclitaxel, are widely used to treat breast cancer, but docetaxel is more frequently used than paclitaxel, particularly in Japan. As far as we have been able to determine, there have been only two case reports describing the effectiveness of weekly paclitaxel therapy in patients, previously treated with docetaxel [19, 20]. And the objective of this study was to evaluate the efficacy, toxicity, and predictive factors for success of weekly paclitaxel therapy in MBC patients previously treated with docetaxel.

Patients and methods

A total of 308 patients with MBC were treated with weekly paclitaxel as salvage chemotherapy between January 1999 and October 2002 at the National Cancer Center Hospital. We retrospectively selected patients who fulfilled the following selection criteria as subjects for the present study: (1) docetaxel administered during prior chemotherapy for MBC; (2) adequate bone marrow and organ function (neutrophils >1500 μ^{-1}, AST <100 IU/l, ALT <100 IU/l, serum creatinine <2.0 mg/dl); (3) written informed consent before treatment. Patient treated with weekly paclitaxel plus trastuzumab combination was excluded.

Patients were intravenously (i.v.) infused with chorpheniramine maleate 10 mg and dexamethazsone 8 mg 30 min before the paclitaxel infusion. Paclitaxel 80 mg/m^2 was administered over a 1-h period weekly. Each 8-week cycle consisted of six consecutive weekly courses of treatment followed by a 2 week rest. Paclitaxel adminstration was repeated until there was evidence of disease progression or until unacceptable toxicity occurred. In the event of serious toxicity, treatment was withheld until recovery.

Patients with no bidimensionally measurable lesions were not eligible for objective response evaluation. Objective responses were evaluated according to WHO criteria [21]. Patients without measurable lesions were classified as not assessable (NA). Toxicity was evaluated according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) ver 2.0.

Statistical analysis

The primary statistical analysis was performed to assess the effect of prior docetaxel response ('CR, PR, and NC' or 'PD') and interval between from the final infusion of docetaxel and disease progression. Since these two factors were highly correlated, we combined them and created a categorical variable (DTX profile) that has three levels: 'primary resistance,' 'secondary resistance' (short interval), and 'secondary resistance (long interval)', and the frequencies of response and non-response to weekly paclitaxel therapy were counted for each of these three levels of the DTX profile. The Cochran–Mantel–Haensxel test was performed for the 3 × 2 contingency table on the assumption that the DTX profile is an ordered categorical variable.

The secondary analysis consisted of a multivariate logistic regression to assess the effect of the following other factors on the response to paclitaxel therapy: DTX profile, performance status, number of organs involved, disease site, the number of prior regimens for MBC.

Time to progression was measured from the first day of treatment until disease progression or

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the final day of the follow-up period without disease progression, and overall survival time was measured from the first day of treatment until death or the final day of the follow-up period. Median time to progression and median overall survival were estimated by the Kaplan–Meier method. The statistical analysis was performed with SAS version 8.2 software (SAS Institute, Cary NC), and the significance level of the results was set at 0.05 level (two-sided).

Results

Patient characteristics

Of the 308 patients treated with weekly paclitaxel in our hospital, 96 patients had received prior docetaxel chemotherapy, and 14 patients of them were excluded based on the selection criteria described above: two patients on the basis of neutrophill count; 11 patients on the basis of liver function; one patient on the basis of serum creatinine value. Ultimately 82 of the 98 patients were included in the analysis. The patient characteristics are listed in Table 1. Median age was 54 years. Forty-one patients had received a regimen as adjuvant chemotherapy. The median number of organs involved was 2 (range: 1–5). The majority of the patients (67.1%) had visceral-dominant disease. Most of the patients (91.5%) had received two or more chemotherapy regimens for MBC. Seventy-six patients had received prior anthracycline-containing chemotherapy for MBC, and their median cumulative anthracycline exposure was 240 mg/m^2 (range: 80–480 mg/m^2). The median number of prior docetaxel cycles was 6 (range: 1–16). Most of the 82 patients (85.4%) had received docetaxel at a dose of 60 mg/m^2. The median cumulative docetaxel exposure in the study was 360 mg/m^2 (range: 120–960 mg/m^2). The median interval between the final infusion of docetaxel and the start of weekly paclitaxel therapy was 2.9 months (range: 0.5–23 months). Median follow-up time was 9.5 months, and the follow-up times ranged from 0.5–39 months.

Table 1. Patient characteristics

	No. of patients (%)
Number	82
Age	
Median	54
ECOG performance status	
0	31
1	36
2	6
≧3	9
No. of organs involved	
1	20
2	31
3	19
≧4	12
Disease sites	
Primary lesion	6
Soft tissue metastasis	32
Lymph node metastasis	36
Liver metastasis	29
Lung metastasis	28
Pleural effusion	23
Bone metastasis	35
Brain metastasis	7
Disease pattern	
Visceral-dominant	54
Non-visceral dominant	28
No. of previous chemotherapy regimens	
1	7
2	57
≧3	18
Prior docetaxel chemotherapy	
Median number of courses	6
Range	1–16
Hormonal status (ER or PgR)	
Positive	38
Negative	31
Unknown	13

Abbreviations: ECOG: Eastern Cooperative Oncology Group; HER2: Human Epidermal Growth Factor Receptor type 2.

Response

The total number of courses of weekly paclitaxel therapy was 909, and the median number of courses was 10 (range: 2–45). The response rate among all 82 patients was 19.5% (Table 2; 4 CR and 12 PR, 95% confidence interval (CI): 10.9–28.1%). Objective response rates according to previous docetaxel treatment profile are listed in Table 2. The differences in response rates between docetaxel treatment profiles (primary resistance, secondary resistance [Short interval], secondary

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Table 2. Objective response rate to weekly paclitaxel according to DTX profile

DTX profile	No. of patients	CR	PR	NC	PD	NA	RR (95% CI)
Primary resistance	24	0	2	10	10	2	8.3% (0–19.4%)
Secondary resistance	58	4	10	29	13	2	24.1% (13.1–35.1%)
Short interval	39	2	5	20	10	2	17.9% (5.9–30.0%)
Long interval	19	2	5	9	3	0	36.8% (15.1–58.5%)
Total no. of patients	82	4	12	39	23	4	19.5% (10.9–28.1%)

Cochran–Mantel–Haenszel test: $p = 0.027$ (primary resistance, short interval, long interval).
Abbreviations: CR: complete response; PR: partial response; NC: no change; PD: progressive disease; NA: not assessable; RR: response rate; CI: confidence interval; Short interval means ≦120 days between the final docetaxel infusion and disease progression. Long interval means > 120 days between the final docetaxel infusion and disease progression. All cases classified as 'primary resistance' experienced disease progression within 120 days of the final docetaxel infusion.

resistance [Long interval]) were statistically significant ($p = 0.0247$, Cochran–Mantel–Haenszel test). The results of the multivariate analyses did not suggested that any other factors affected the response to weekly paclitaxel treatment (Table 3). The median time to progression was 3.7 months (Figure 1; 95% CI: 2.75–4.72 months). Median overall survival was 9.4 months (Figure 1; 95% CI: 7.25–11.55 months).

Toxicity

A total of 909 courses in the 82 patients were assessable for toxic effects. The median cumulative dose of paclitaxel was 800 mg/m^2 (range: 160–3600 mg/m^2). The paclitaxel dosage was reduced in five patients due to toxicities: Grade 4 neutropenia in 2; Grade 3 fatigue in 1, Grade 3 diarrhea in 1; and Grade 3 neuropathy in 1. The toxicity profiles are listed in Table 4. Weekly paclitaxel treatment was generally well tolerated and manageable in an outpatient setting. Although grade 3 or 4 netropenia occurred in 10 patients (12.2%), no febrile neutropenia was observed. Neurosensory toxicity was observed in 51 patients (62.2%). No grade 4 non-hematological toxicity was reported, and there were no unexpected adverse reactions or treatment-related deaths.

Discussion

This study evaluated the efficacy and safety profile of weekly paclitaxel in docetaxel resistant MBC patients.

Table 3. Multivariate analyses of weekly paclitaxel response according to variables before weekly paclitaxel therapy (logistic regression model)

Variables before WPTX therapy	Odds ratio	95%CIs	*p* value
DTX profiles			
'Primary resistance':'Long interval'	0.131	0.022–0.773	0.0248
'Short interval':'Long interval'	0.368	0.101–1.339	0.1292
Performance status			
0-2:3-4	0.755	0.113–5.038	0.7716
Number of organs involved			
≧3:1–2	0.481	0.130–1.776	0.2723
Disease pattern			
Visceral:Non-visceral	1.276	0.345–4.720	0.7152
Number of prior regimens for MBC			
≧3:1–2	0.845	0.196–3.643	0.8212

Abbreviations: WPTX: weekly paclitaxel therapy.

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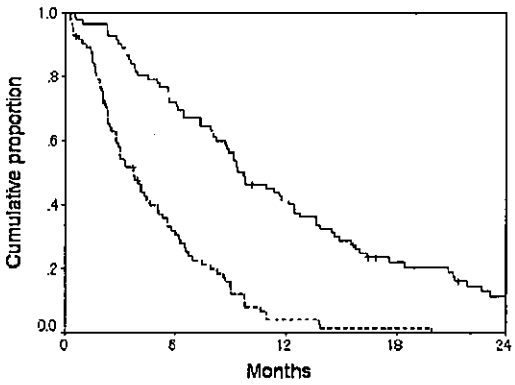

Figure 1. Kaplan–Meier analysis of time to progression (dots line) and overall survival (solid line). Vertical bars indicate censored cases.

Table 4. Maximum grade toxicity (% of patients)

	Maximum grade (NCI-CTC ver 2.0) % of patients			
	1	2	3	4
Leukopenia	36.6	30.5	8.5	0
Neutropenia	28	25.6	9.8	2.4
Anemia	36.6	14.6	4.9	0
Thrombocytopenia	1.2	0	0	0
Fatigue	23.1	3.7	1.2	0
Appetite loss	18.3	3.7	0	0
Nausea	23.2	0	1.2	0
Vomiting	14.6	0	1.2	0
Stomatitis	1.2	1.2	0	0
Diarrhea	3.7	0	1.2	0
Arthalgia/myalgia	4.9	2.4	0	0
HSR	7.3	3.7	0	0
Neurosensory	52.4	9.8	0	0

Abbreviations: HSR: hypersensitivity reactions.

The definition of resistance to docetaxel referred to various definitions of drug resistance had been used in previous reports [12, 14, 18, 22]. The overall objective response rate was 19.5%, and the response rate was higher in the secondary-resistance patients than in the primary-resistance patients (24.1 versus 8.3%), but the difference did not reach statistical significance. On the other hand, the interval between the final infusion of docetaxel and disease progression was a statistically significant predictor of response to the weekly paclitaxel. Previous studies on breast, ovarian and small-cell lung cancer described sensitive relapse were defined patients who relapse more than 3–6 months following completion of primary chemotherapy, and can be effectively retreated with same regimen or second-line chemotherapy [12, 22, 23]. Our result was attributable to the tumor biology of chemo-resistant as sensitive or refractory recurrence.

The results of study showed that weekly paclitaxel is modestly active in patients with docetaxel-resistant MBC and showed definite partial cross-resistance between paclitaxel and docetaxel, as reported previously in pre-clinical and clinical studies [9, 10, 17, 18]. Our study may be criticized for not a prospective study, but the overall objective response rate of 19.5% was almost the same as the overall response rates to docetaxel treatment in paclitaxel-resistant populations (18.1, 25%) [17, 18]. The response rate to weekly paclitaxel treatment in the primary docetaxel-resistance patients was poor than docetaxel treatment in the primary paclitaxel-resistance patients (8.3 versus 17.6, 20%) [17, 18]. In pre-clinical study, docetaxel exhibited greator cytotoxicity in paclitaxel-resistant cells [24]. Docetaxel has reported to be more active than paclitaxel against multi-drug resistance protein-expressing tumor [25]. Considering these findings it is reasonable that, there might be difference in the response in each primary resistant patient. We think that paclitaxel might not be useful in patients with primary docetaxel resistance.

In the present study, most patients were heavily treated MBC patients, and as a result the incidence of neutropenia (of any grade) was slightly higher than in previous studies of weekly paclitaxel in patients with anthracycline-refractory disease, however, the incidence of severe neutropenia (grade 3 or more) was comparable [15, 16]. By contrast, the incidence of paclitaxel-associated neurosensory toxicity was similar to its incidence in the previous studies [15, 16]. Therefore, weekly paclitaxel was almost feasible treatment in outpatient setting, even if heavily treated MBC patients.

In conclusion, weekly paclitaxel therapy (80 mg/m^2) was modest effecacy in patient with docetaxel resistant MBC. However, the response rate of weekly paclitaxel therapy in primary resistance was clearly lower than that of patients with short and long interval. Therefore, weekly paclitaxel therapy should not be recommended for primary resistance patients with docetaxel.