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AUTHOR'S PROOF!

Breast Cancer Research and Treatment **00:** 1–6, 2004.

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 Recepter 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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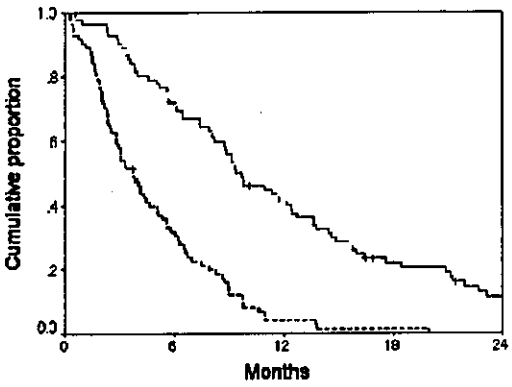

Figure 1. Kaplan-Meier analysis of time to progression (dots line) and overall survival (solid line). Vertical bars indicate censored cases.

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.

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Journal : BREA | Dispatch : 19-7-2004 | Pages : 6
PIPS No. : D000001265 | LE | TYPESET
MS Code : BREA 470 | CP | DISK

Expression of Insulin-Like Growth Factor 1 Receptor in Primary Breast Cancer: Immunohistochemical Analysis

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Insulin-like growth factor-1 receptor (IGF-1R) has been implicated in regulation in tumor growth. The results of previous studies performed by radioimmunoassay are conflicting, and the prognostic significance of IGF-1R expression in primary breast cancer is still controversial. IGF-1R expression was evaluated in formalin-fixed, paraffin-embedded tissue of 210 primary breast cancer patients by using anti-IGF-1R antibody. The clinicopathologic variables and 5-year disease-free survival were studied, and their correlations between IGF-1R expressions were investigated. IGF-1R overexpression was observed in 43.8% of tumors. IGF-1R overexpression had no correlation with prognosis or with other clinicopathologic parameters, such as age, tumor size, nodal status, histologic grade, hormone receptor status, and human epidermal growth factor 2 status. Though its prognostic value in breast cancer is limited, immunohistochemical evaluation of IGF-1R by using this monoclonal antibody may be useful in translational research using archived material. HUM PATHOL. 35:1537-1542. © 2004 Elsevier Inc. All rights reserved.

Key words: Insulin-like growth factor 1 receptor, immunohistochemistry, primary breast cancer, prognostic marker.

Abbreviations: IGF-1R, insulin-like growth factor-1 receptor; IGFBPs, IGF-binding proteins; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor 2; IHC, immunohistochemistry; DFS, disease-free survival; RIA, radioimmunoassay.

IGF-1R is a glycosylated heterotetramer composed of 2 extracellular α-subunits and β-subunits that have intrinsic tyrosine kinase activity with 70% homology to the insulin receptor.[1] IGF-1R mainly mediates the effect of insulin-like growth factors (IGFs), which are potent mitogens that regulate cell proliferation, differentiation, and protection from apoptosis.[2] The clinical and epidemiologic data suggest that the levels of IGF-1 or IGF binding proteins (IGFBPs) in the serum are related to the risk of solid tumors such as breast, prostate, endometrial, ovarian, and colon cancer.[3]

IGF-1R has been found to be significantly expressed and highly activated in breast cancer, and its prognostic and predictive value in clinical samples are of interest.[4-8] There are several methods to measure IGF-1R expression: radioimmunoassay, Western blotting, and immunohistochemistry (IHC). Immunohistochemical evaluation is the most simple and the easiest to perform. To date, there are several commercially available anti-IGF-1R antibodies, but there are no established scoring methods for IGF-1R expression in formalin-fixed, paraffin-embedded tissue. We herein report the prognostic significance of IGF-1R overexpression as determined by IHC on archive materials of consecutive primary breast cancer patients when evaluated by the intensity of membrane staining. We also investigated its correlation with various clinicopathologic factors.

MATERIALS AND METHODS

Patients

This study was performed on 276 consecutive primary breast cancer patients who underwent surgery or biopsy at National Cancer Center Hospital from January to December 1997. From the cases, 268 paraffin-embedded formalin fixed tissues were obtained. Thirteen stage IV breast cancer patients, 9 patients with malignancy of other origin, 7 metachronous bilateral breast cancer patients, 4 synchronous breast cancer patients, and cases impossible for evaluation in invasive component such as ductal carcinoma in situ were excluded from analysis. Thus immunohistochemical staining was performed on 210 invasive carcinomas.

Pathology

Tumor size, number of axillary lymph node metastasis, histologic type, and histologic grade according to Nottingham combined histologic grading were noted.

Immunohistochemistry

IHC was performed for estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor 2 (HER2), and IGF-1R on 4-μm-thick serial sections from formalin-fixed, paraffin-embedded tissue.

Monoclonal antibodies 1D5 (DAKO) and 1A6(DAKO) were used for ER and PR IHC, respectively, according to the recommended staining protocol by the manufacturer. It was scored to be positive when $\geq$10% of the cancer cells were

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0046-8177/$—see front matter

doi:10.1016/j.humpath.2004.09.005

TABLE 1. Scoring of Insulin-Like Growth Factor-1 Receptor Expression According to Intensity of Membrane Staining

Score	Pattern of Immunohistochemical Staining in Invasive Component
0	No staining observed or staining observed in <10% of tumor cells.
1+	A faint or barely perceptible membrane staining in >10% of tumor cells. The cells are only stained in part of their membrane.
2+	A weak to moderate complete membrane staining in >10% of tumor cells.
3+	A strong complete membrane staining in >10% of tumor cells.

stained. Herceptest (DAKO) was used for HER2 assay as described elsewhere, and (2+) and (3+) was defined as overexpression.[9]

The primary antibody for IGF-1R used in this study (clone 24-31) is a mouse monoclonal antibody that is specific for α-subunit of human IGF-1R.[10] Paraffin sections were retrieved in distilled water at 95°C for 40 minutes. Then the sections were incubated with the anti-IGF1R antibody for 30 minutes and were rinsed in EnVision plus (DAKO) for 30 minutes. The reaction product was made visible after incubation in diaminobenzidine for 10 minutes.

Human normal colon mucosa and breast cancer–cultured cellblock was used as positive control. The IGF-1R expression in human colon mucosa was defined as (1+), and we scored (2+), (3+) according to the intensity of the membrane-staining within invasive component in accordance to scoring of HER2 by HercepTest (Table 1, Fig 1) at magnification of ×100 to ×200. When there was heterogeneity in IGF-1R staining within a tumor, the highest score was applied regardless of its area among the tumor.

Statistical Analysis

The results were statistically evaluated by SAS software (version 8.2; SAS Institute Inc, Cary, NC).

Disease-free survival (DFS) was calculated from the date of surgical excision of the primary tumor to the date of recurrence or last follow-up. Prognostic information was masked to the pathologists responsible for evaluation of biologic markers. DFS was calculated for all 210 cases. DFS curves were computed by the Kaplan-Meier method. Correlation between IGF-1R expression and various clinicopathologic factors were analyzed by using Fisher's exact test. Univariate analysis of DFS was performed with the use of log-rank test. P values of less than 0.05 were considered to be statistically significant.

RESULTS

Characteristics of the Patients

The median age of study population was 53 years (range, 25-83). The median diameter of invasion was 2.2 cm (range 0.1 to 14.0). The majority of the histologic type was invasive ductal carcinoma. About half of the cases were node negative. The number of cases with Nottingham combined histologic grade 1, 2, and 3 were 12, 37, and 137 cases, respectively.

ER and PR was positive in 154 (73.3%) and 98 (46.7%) tumors. HER2 overexpression was seen in 36 tumors (17.1%; 2+: 2.9%, 3+: 14.2%). See Table 2 for a summary of data on patient characteristics.

IGF-1R Immunohistochemistry

IGF-1R was localized to epithelial compartment including normal breast epithelium, ductal carcinoma in situ, and invasive carcinoma (Fig 1). A weak to moderate (ie, (1+) or (2+)) staining was observed in normal duct epithelium. The majority of invasive carcinoma showed both cytoplasmic and membrane staining. There was heterogeneity of staining inside the same tumor: sporadic or patchy, focal, and diffuse pattern. Heterogeneity of IGF-1R staining was observed in 61 (29%) of 210 cases. Though this intratumoral heterogeneity made scoring difficult in some cases, immunohistochemical staining of IGF-1R was stable and reproducible. The number of cases of IGF-1R score 0, 1+, 2+, 3+ was 24 (11.4%), 94 (44.8%), 25 (11.9%), and 67 (31.9%), respectively.

IGF-1R Expression in Association With Various Clinicopathologic Parameters

There was no correlation between IGF-1R expression and age, size of invasion, presence or absence of axillary lymph node metastasis, and histologic grade. ER, PR, and HER2 status also did not correlate with IGF-1R expression. See Table 3.

Univariate Analysis

The median follow-up period was 5.0 years. The 5-year DFS was significantly better among patients with positive ER expression, and negative HER2 overexpression (Table 4). The patients with invasion less than 2 cm, negative axillary lymph node and positive PR expression had a trend of better prognosis, though it did not reach statistical significance. IGF-1R expression status did not correlate with DFS (Fig 2).

DISCUSSION

We tested the prognostic significance of IGF-1R overexpression on formalin-fixed, paraffin-embedded tissue and found no correlation between IGF-1R expression in primary tumor and 5-year DFS. Because this monoclonal antibody is specific[10] and prognostic value of other known biologic markers was validated within this patient population, we conclude that IGF-1R overexpression has no impact on prognosis of breast cancer in this study. This result is concordant with the Foekins et al[4] report, in which IGF-1R was evaluated in 214 primary breast cancer by ^{125}I-IGF radioimmunoassay (RIA).

Estimates of the proportion of IGF-1R expression that have been derived from previous studies, mostly performed by RIA, vary from 39% to 93%.[5-8] This range of positivity may be due to the sensitivity of RIA, because strong membrane staining of 2+ and 3+ was seen

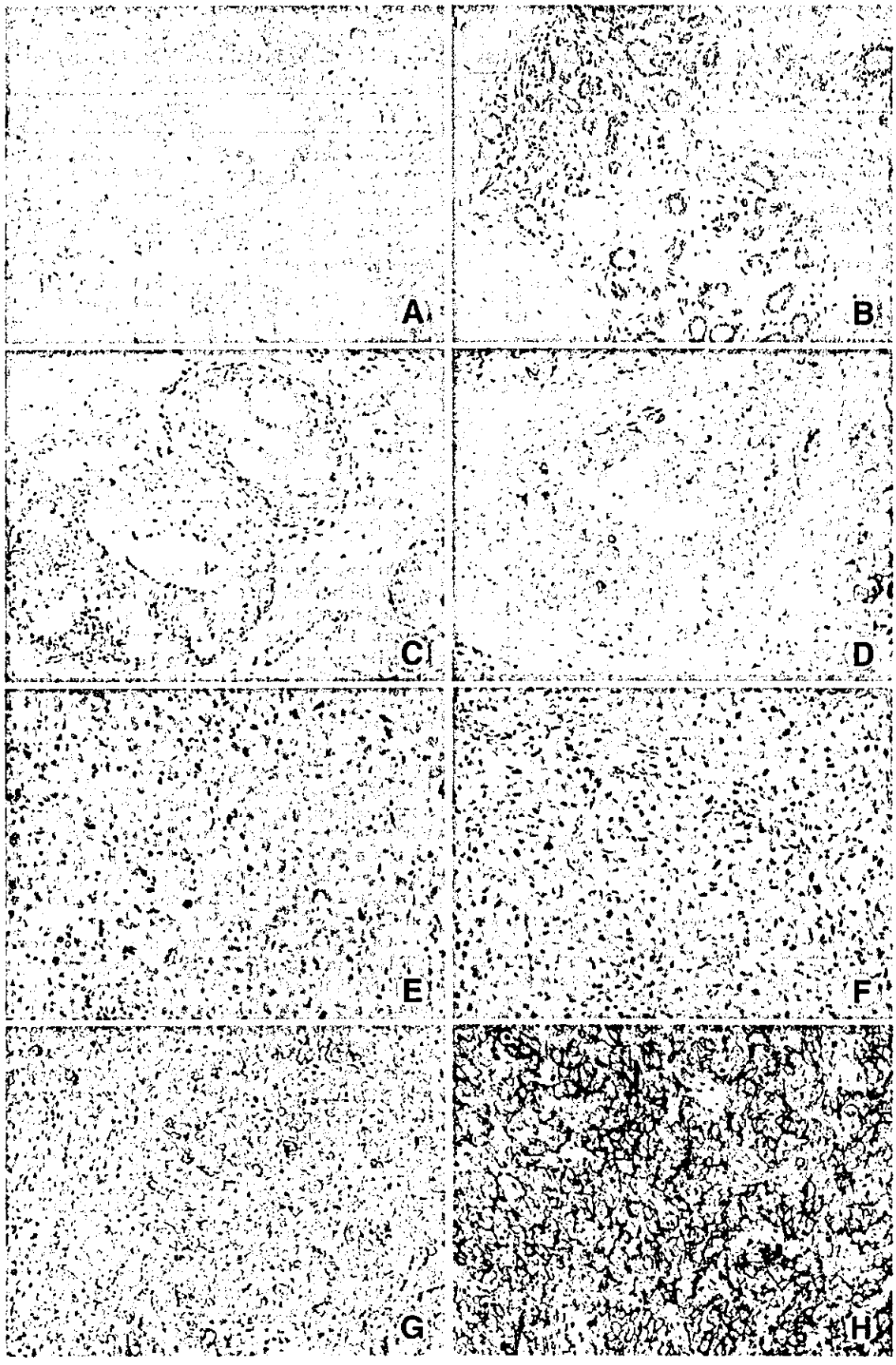

FIGURE 1. Immunohistologic staining of insulin-like growth factor-1 receptor in (A and B) normal epithelium, (C and D) ductal carcinoma in situ, and invasive ductal carcinoma (E-H). IGF-1 receptor expression was scored according to area and intensity of membrane staining (E: score = 0; F: 1+; G: 2+; H: 3+; original magnification, ×100)

TABLE 2. Characteristics of the Patients and Tumors

Parameters	Data
Total	210
Age in yr, range (median)	25-82 (51)
Size of invasion in cm, range (median)	0.1-14.0 (2.2)
Histologic type	
Invasive ductal carcinoma	19
Invasive lobular carcinoma	7
Others	6
Histologic grade	
Grade 1	10
Grade 2	80
Grade 3	120
Axillary lymph node status	
Positive	95
Negative	112
Unknown	3
ER	
Positive	154
Negative	56
PR	
Positive	98
Negative	112
HER2	
0-1	174
2	6
3	30
IGF-1R	
0	24
1	94
2	25
3	67

NOTE. Data are n unless otherwise indicated.

Abbreviations: ER, estrogen receptor, PR, progesterone receptor; HER2, human epidermal growth factor 2; IGF-1R, insulin-like growth factor-1 receptor.

in 43.8%, whereas almost 90% of invasive carcinoma showed moderate staining (scores 1, 2, and 3) in our observation. Happerfield et al[11] reported the localization of IGF-1R staining in benign and malignant fresh-frozen tissue by using monoclonal antibody α-IR3 and found high-intensity labeling in all normal mammary epithelium with an intensity that matches that of carcinomas. They observed membrane, cytoplasmic, and mixed staining patterns, which was concordant with our observation. We scored IGF-1R expression according to the intensity of membranous staining, but the role of cytoplasmic IGF-1R has yet to be clarified.

TABLE 3. Correlation Between Various Factors and IGF-1R IHC score (0/1 vs. 2/3)

Parameters	IHC Score 0/1+	IHC Score 2+/3+	Odds Ratio (95% CI)	Fisher's Exact Test (*P*)
Lymph node status			1.347 (.776-2.337)	.3268
Positive	49	46		
Negative	66	46		
Age (yr)			.932 (.536-1.620)	.8878
<50	51	41		
≥50	67	51		
ER			1.165 (.627-2.165)	.6413
Positive	85	69		
Negative	33	23		
PR			1.174 (.680-2.028)	.5800
Positive	53	45		
Negative	65	47		
HER2			1.032 (.501-2.125)	1.000
0-1	98	76		
2-3	20	16		

Abbreviations: IGF-1R, insulin-like growth factor-1 receptor; IHC, immunohistochemistry; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor 2.

TABLE 4. Univariate Analysis of DFS by Various Clinicopathologic Parameters

Parameters	5-yr DFS (%)	*P* Values
Lymph node status		0.0670
Positive	68.4	
Negative	79.5	
Age (yr)		
<50	78.3	0.6194
≥50	71.2	
Size of invasion (cm)		0.0667
<2.0	84.3	
≥2.0	66.4	
ER		0.0290
Positive	77.3	
Negative	66.1	
PR		0.1269
Positive	83.7	
Negative	66.1	
HER2		0.0483
0-1	78.4	
2-3	47.2	

Abbreviations: DFS, disease-free survival; ER, estrogen receptor, PR, progesterone receptor; HER2, human epidermal growth factor 2.

There are several other reports discussing the prognostic value of IGF-1R expression determined by RIA in primary breast cancer. Findings are contradictory: Foekins et al found no relationship between IGF-1R levels,[4] whereas Bonneterre et al[6] and 2 other groups reported IGF-1R as a favorable prognostic factor.[7,8] Because sensitivity of RIA has wide discrepancy as mentioned earlier, further studies by IHC are warranted.

Ouban et al[12] showed the overexpression of IGF-1R by using anti-IGF-1R polyclonal antibody toward the β-subunit of the human IGF-1R in variety of human carcinomas. Bhatavdekar et al[13] suggested that IGF-1R–negative tumor with concomitant hyperprolactinemia might indicate unfavorable prognosis in advanced colorectal cancer. Some data show prevalence of serum or tumor IGF-BP3 within clinical outcome in malignancy, such as breast and prostate cancer.[14,15] In Ewing sarcoma, there was a trend toward increased survival in a high IGF-BP3 to IGF-1 ratio.[16] Because biology of IGF-1R is regulated by a complex endocrine and paracrine system that involves various humoral and local factors, we should take into account those multiple factors that may affect IGF-1R in future studies.

In this study, there was no correlation between IGF-1R expression and ER, PR, or HER2 expression. In previous clinical studies in breast cancer, IGF-1R expression has been reported to have positive correlation with ER expression.[17] However, ER was not necessarily coexpressed in IGF-1R–overexpressed cells in serial sec-

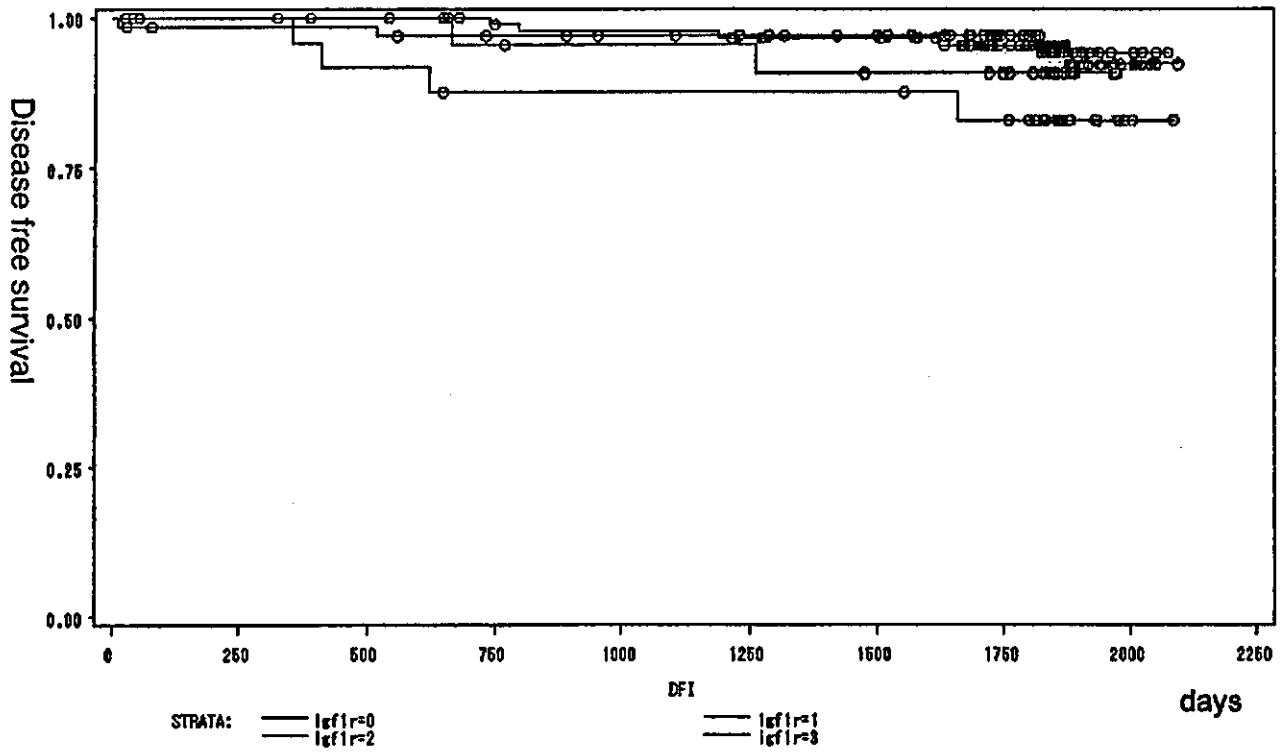

FIGURE 2. Disease-free survival curves for patients group according to insulin-like growth factor-1 receptor expression.

tions in our study. In cellular experiments, there are growing evidences that support reciprocal interaction between estrogens and IGF-1R or between IGF-1 and ER.[18] In terms of HER2, Balana et al[19] suggested existence of hierarchical interaction between IGF-1R and HER2 in regard to HER2 phosphorylation. Multiple signaling pathways are involved in regulation of breast cancer proliferation, apoptosis and metastasis. Technologies such as cDNA array may be useful in understanding the role of IGF pathways in breast cancer.[20]

Though impact of IGF-1R expression on prognosis seems to be limited, IHC is a clinically useful tool for examining protein expression in archive materials. It also resolves the issues of localization and heterogeneity within the tissue. Moreover, blockade of IGF signaling pathway represents an attractive targeted therapy. Preclinical studies of IGF-1R targeted therapy, such as antisense strategies, have shown promising anti-tumor effect, and some are currently under clinical trials.[21-23] Determination of IGF-1R expression by IHC has potential in clinical use in selecting a particular subset of patients that may benefit from IGF-1R targeted therapy.

Acknowledgment. The authors are grateful to Dr. Yuki Kamihara (DAKO Cytomation, Inc) for her contribution in tissue preparation.

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Re: Insulinlike growth factor 1 receptor: predictive factor in breast cancer patients treated with trastuzumab?

To the Editor,

The mechanism of resistance to trastuzumab, either inherent or acquired, is critical in improving the prognosis of HER2-overexpressing metastatic breast cancer patients, but there is limited knowledge from in vitro experiments. Testing a preclinical hypothesis in clinical samples is crucial.

We recently tested the relationship between insulinlike growth factor-1 receptor (IGF-1R) protein expression and the efficacy of trastuzumab in hormone-resistant, chemotherapy-naive, metastatic breast cancer patients, with a hypothesis that IGF-1R overexpression might correlate with trastuzumab resistance [1]. IGF-1R expression was immunohistochemically measured in 26 formalin-fixed paraffin-embedded tissue specimens from primary or metastatic lesions of patients treated with single-agent trastuzumab using a mouse monoclonal antibody clone 24-31 [2]. As a result, patients with higher IGF-1R expression demonstrated a trend toward longer duration of trastuzumab therapy but did not correlate with the clinical response to trastuzumab. Although limited by the nature of a small retrospective study, the result suggests that IGF-1R protein expression itself may not be the major determinant of the resistance to, or efficacy of, trastuzumab in HER2-overexpressing tumors.

Lu et al [3,4] demonstrated in human breast cancer cell lines that an increased level of IGF-1R signaling adversely interferes with the action of trastuzumab on cell growth and that IGF-1R blockade can restore its sensitivity. They observed a dose-response enhancement of trastuzumab-induced growth inhibition by the addition of IGF-BP3, which physiologically interferes with the ligand-receptor interaction of IGF-1 [3]. On the other hand, Nahta et al [5] reported that down-regulation of p27(kip1) may be associated with trastuzumab resistance in breast cancer cells. p27(kip1) is a distal downstream effecter of growth factor pathways including EGFR, HER2, and IGF-1R pathways. It is possible that both upstream regulations of IGF-1R and downstream cross-talk with other signaling pathways are involved in trastuzumab resistance. As Altundag et al [6] state, further studies are necessary to clarify the role of the IGF-1R axis in the biology and therapeutics of HER2-overexpressing breast cancer.

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DOI of original article: 10.1016/j.humpath.2005.02.008

0046-8177/$ – see front matter © 2005 Published by Elsevier Inc
doi:10.1016/j.humpath.2005.02.009

Virchows Arch (2004) 445:421–424
DOI 10.1007/s00428-004-1082-5

CASE REPORT

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Second primary osteosarcoma with rosette-like structure in a patient with retinoblastoma

Received: 4 February 2004 / Accepted: 15 June 2004 / Published online: 28 July 2004

Abstract A Japanese male patient developed bilateral retinoblastomas at the age of 1 year, but remained continuously disease-free after enucleation of the left eye and radiation therapy to the right eye. He noticed a painless hard mass around the right temporal bone when he was 25 years old. Biopsy specimen showed a small multinodular proliferation of tumor cells with prominent rosette-like structures. Eosinophilic material with focal mineralization was seen in the center of the rosettes. Immunostaining of the tumor cells showed positive reactions for epithelial membrane antigens CD 56 and CD 99. The patient was treated with systemic chemotherapy, and the tumor partially diminished. It is well known that a few osteosarcomas show a rosette-like appearance with production of osteoid in the center, but this is the first case of second primary osteosarcoma with prominent rosette-like features.

Keywords Second primary osteosarcoma · Retinoblastoma · Rosette · Diagnosis

Introduction

Retinoblastoma is a malignant neoplasm in childhood occurring in 1/15,000 to 1/30,000 live births. Improved treatment for retinoblastoma together with early diagnosis has resulted in the cure of an increasing number of patients [17]. It has long been established that children affected by retinoblastoma have a high risk for the development of second primary malignant lesions. The majority of these second primary malignancies are osteosarcomas and soft-tissue sarcomas [1, 11, 14].

Second primary sarcomas after retinoblastoma may be related to prior radiation therapy for the original retinoblastoma [5, 6, 12]. In patients previously irradiated for bilateral or familial unilateral retinoblastoma, 70% of second malignancies have occurred within the radiation field, while 30% occurred outside the field of radiation [1]. Differential diagnosis between these second primary sarcomas and recurrent retinoblastoma may be problematic [19].

Recently, we encountered a 25-year-old Japanese man with a second primary osteosarcoma within the prior radiation field. Peculiarly, this lesion showed rosette-like features that have not been described in previous literature in a second primary osteosarcoma. We, therefore, present here a case requiring special attention during the differential diagnosis of osteosarcoma with rosette-like features from recurrence of retinoblastoma.

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Clinical history

A Japanese male patient was diagnosed with bilateral retinoblastomas at the age of 1 year and underwent enucleation of the left eye and radiation therapy with 49 Gy to the right eye. He had remained continuously disease-free after the treatments. Both his father and mother had a history of retinoblastoma. When he was 25 years old, he noticed a painless hard mass around the right temporal bone. Axial computed tomography showed a well mineralized mass (arrow) on the temporal bone associated with focal subarachnoid hemorrhage (arrowheads, Fig. 1). Axial T1-weighted magnetic resonance (MR) images showed a mass of iso signal intensity relative to white matter. On T2-weighted MR images, the tumor showed heterogeneous and high signal intensity relative to white matter. Multiple fluid levels suggesting the presence of intratumoral hemorrhage were also observed (arrows, Fig. 2A, B). Laboratory data, including peripheral blood count, alkaline phosphatase, and C-reactive protein, were within the normal range. Clinical