

c-erbB-2

Immunohistochemical Expression of c-erbB-2 Protein in Breast Cancer

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Purpose: A clinical trial that evaluated the efficacy of Herceptin[®] (anti-erbB2 antibody) as a first-line therapy for metastatic breast cancer was presented. It was demonstrated that 38% of the metastatic breast cancer patients benefited clinically from the Herceptin therapy. Recently, a trial of systemic chemotherapy was recommended as a first-line treatment for the patient with metastatic breast cancer refractory to Herceptin therapy. Therefore, it is necessary to evaluate c-erbB-2 protein expression in breast cancer prior to Herceptin treatment and the significance of c-erbB-2 protein as a prognostic predictor.

Methods: To evaluate c-erbB-2 protein as a prognostic predictor, we analyzed the expression of c-erbB-2 protein by the immunohistochemical method in comparison with other factors such as age, tumor size, stage, histologic grade, LN status, hormonal receptor status and DNA ploidy. Then we performed survival analysis. A total of 266 patients who underwent mastectomy between May 1998 and April 2000 were evaluated and statistical significance was determined by χ^2 test.

Results: In 146 of the 266 patients (54.9%) c-erbB-2 was positive in the tumor, and negative in the remaining 120. The overexpression of c-erbB-2 was positively correlated with tumor size and progesterone receptor positivity. The c-erbB-2 expression showed an association with a low recurrence-free survival probability in univariate analysis ($P=0.0159$). However, in multivariate analysis, c-erbB-2 expression was not an independent prognostic factor.

Conclusion: The c-erbB-2 protein expression appears to have prognostic significance in breast cancer but long-term follow-up studies are necessary for confirmation. (J Korean Surg Soc 2002;62:456-462)

Key Words: c-erbB-2, Breast cancer
: c-erbB-2

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가
 가 가 (1)
 가
 30% 가 (2-4)
 가
 c-erbB-2 (HER2, HER2/neu) HER family
 Epidermal growth factor receptor
 (EGFR), HER3 HER4가 (5)
 가 c-erbB-2
 (6, 7)
 Herceptin[®] (erbB-2)
) 1 가
 (8) c-erbB-2 38%
 1 Herceptin[®]
 c-erbB-2

가 , 0.3% 15 Tris
 3
 normal horse serum 30 rabbit
 anti-human c-erbB-2 oncoprotein (DAKO, Denmark, 1 : 100)
 , chamber 4°C
 TBS 3
 (Vector Elite kit, Vector Laboratories, USA) 30
 ABC (avidin-biotin conjugate) reagent
 45 TBS Tris-HCl
 (pH 7.6) diaminobenzidine tetrachlo-
 ride (DAB, Sigma Chemicals, USA) 2 3
 10% Mayer's hematoxylin

1)
 1998 5 2000 4
 266
 2001 5 31
 24.9 (: 4 37)
 , DNA ploidy,
 c-erbB-2 가 c-
 erbB-2 가

2)
 (1) : 가
 4 μm
 organosaline (probe-on plus
 slide, Fisher Scientific, USA) 100% xylene
 100%, 90% 75%
 . Microwave 10 mM citrate
 buffer (pH 6.0) 750 watt 5 가
 5 2 가 20
 tris
 buffered saline (TBS, 50 mM, pH 7.4)

(2) : c-erbB-2
 가
 0 (Fig. 1), 10%
 1 (+), 50% 2 (++)
 (Fig. 2), 50% 3 (+++)
 (Fig. 3), 4 (++++)
 (Fig. 4)
 가
 (3) : c-erbB-2
 chi-square
 Kaplan-Meier
 Log rank test
 Cox-proportional hazard model
 P < 0.05

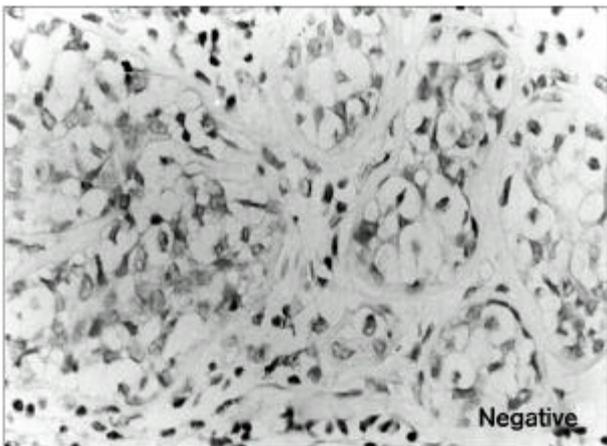


Fig. 1. Breast cancer cells with a negative membrane staining for c-erbB-2, ×400.

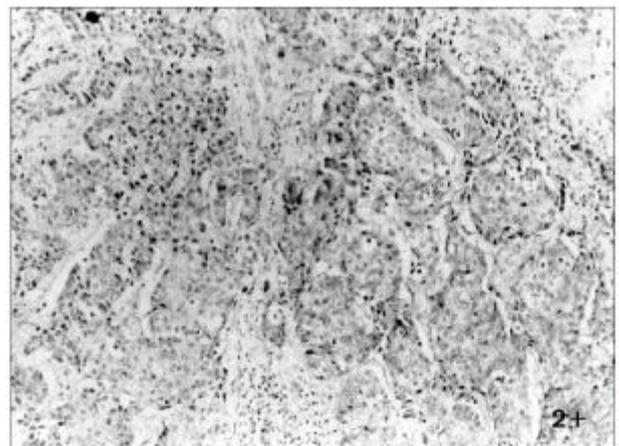


Fig. 2. Breast cancer cells with 2 positive membrane staining for c-erbB-2, ×100.



Fig. 3. Breast cancer cells with 3 positive membranous staining for c-erbB-2, ×100.

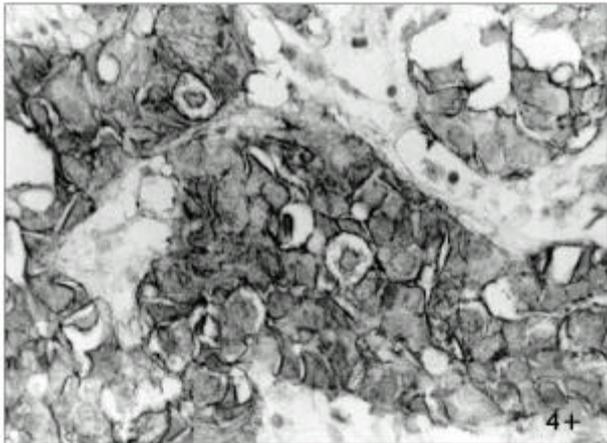


Fig. 4. Breast cancer cells with 4 positive membranous staining for c-erbB-2, ×400.

Table 1. Patient characteristics

Total number of patients	266 (%)
Age in years	48.7± 10.9 (24 78)
Clinical tumor size (cm)	3.0± 1.8 (0.3 9.0)
Clinical stage	
0	16 (6.0)
I	72 (27.1)
IIa	92 (34.6)
IIb	65 (24.4)
IIIa	21 (7.9)
Histologic grade	
I	34 (16.3)
II	134 (62.3)
III	46 (21.4)
No. of positive axillary nodes	
0	170 (63.9)
1-3	52 (19.5)
4-9	20 (7.5)
≥ 10	24 (9.0)
Hormonal receptor status	
Estrogen receptor (ER)	Negative 150 (56.2) Positive 116 (43.8)
Progesteron receptor (PR)	Negative 144 (53.9) Positive 122 (46.1)
C-erbB-2 protein	
0	120 (45.1)
+	36 (13.5)
++	48 (18.0)
+++	44 (16.5)
++++	18 (6.8)
DNA status	
Aneuploid	66 (24.8)
Diploid	65 (24.4)
Unknown	135 (50.7)
Diagnosis	
Ductal calcinoma in situ	17 (6.4)
Infiltrating ductal carcinoma	222 (83.1)
Lobular carcinoma	9 (3.4)
Special type*	19 (7.1)

*Medullary carcinoma, mucinous carcinoma etc.

1)

266 24

78 48.7 .

IIa 가 92 (34.6%) 가

, 170 (63.9%) .

116 (43.8%)가 ,

122 (46.1%) . 222

(83.1%) , 17

(6.4%), 9 (3.4%),

. c-erbB-2 146 (54.9%),

120 (45.1%) (Table 1).

2) c-erbB-2

54 54

54 181 104 (57.5%) c-erbB-2

, 55 85 42 (49.5%) c-erbB-2

. 가 3

cm 191 96 (50.3%) c-erbB-2

3 cm 75 50 (66.7%)가 c-erbB-2

가 , c-erbB-2 (HER2 HER2/neu) Epidermal erbB-2 Allred 17 c-erbB2
HER family growth factor receptor (EGFR), HER3 HER4가 가 c-erbB-2 60.1% c-
(5) 가 , c-erbB-2
185 kd 가 . c-erbB-2 가 가
17q21 4.8 kb mRNA 가
185 kd tyrosine kinase activity 가
가 (6,11) c-erbB-2 가 , DNA ploidy ,
가 가 c-erbB-2
c-erbB-2 polyclonal antibody (sensi- 가 (6,22) c-erbB-2
monoclonal antibody scoring system 가 (20,23) (10,20,21)
fluorescence in-situ hybridisation (FISH) polymerase chain reaction (PCR) c-erbB-2 가 (6,20,22,23) c-erbB-2
Ratcliffe (14) 가 c-erbB-2 , DNA ploidy,
FISH 가 c-erbB-2 c-erbB-2
FISH 가 가 가 c-erbB-2
c-erbB2 transcriptional 가 c-erbB-2
post-transcriptional deregulation (15-17) 가 c-erbB-2
Slamon (6) 189 가 c-erbB-2 가 c-erbB-2
30% c-erbB-2 (23-25) 가 (21,22)
가 c-erbB-2
30% c-erbB-2 20 c-erbB-2 가
54.9% 가 c-erbB-2
가 c-erbB-2 (6,7)
c-erbB-2 가 (23)
3 c-erbB-2
Al- c-erbB-2 c-erbB-2
(12) c-erbB-2 가 c-erbB-2
가 가 c-erbB-2 가
가 c-erbB-2 가
. c-erbB-2

Tamoxifen 가 가 가 c-erbB-2
 (26) Carlomagno (27) c-erbB-2 가 Tamoxifen
 xifen 가
 ER p185^{HER2} . c-erbB-2
 Gusterson (7) c-erbB-2
 CMF (cyclophosphamide, methotrexate, fluorouracil)
 , CAF
 (cyclophosphamide, doxorubicin, fluorouracil)
 c-erbB-2
 .(28,29)
 c-erbB-2 가
 c-erbB-2 anthracycline
 paclitaxel 가
 Herceptin[®] (erbB-2
) first-line
 Gerhard(30) FDA HercepTest[®] (Dako) 3+
 (range: 0 3+) Herceptin[®] therapy , 2+
 FISH Herceptin[®] therapy
 c-erbB-2
 c-erbB-2
 가 FISH concordance test가

c-erbB-2 54.9% ,
 c-erbB-2 가 ,
 c-erbB-2 ,
 , DNA ploidy 가 .
 c-erbB-2 가
 98.33%, c-erbB-2 가 91.78% c-erbB-2
 가 (P=
 0.0159)
 FISH
 c-erbB-2

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