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HER-2양성 유방암 환자의 임상 병리학적 특징 및 생존율 분석

류동원 · 이충한

고신대학교 복음병원 외과학교실

The Clinicopathologic Characteristics of HER-2 Type Breast Carcinoma

Dong-Won Ryu · Chung-Han Lee

Department of Surgery, Kosin University College of Medicine, Busan, Korea

Abstract

목적: The human epidermal growth factor receptor type-2 (ERBB-2)는 대개 ‘‘HER-2/neu’’로 알려져 있고유방암세포의 25~30%에서 표현이 증가되는 것으로 보고되고 있으며 17번 염색체에 위치하여 세포막의 수용체를 나타내는유전자로 알려져 있다. 특히 유방암은 이질적인 병으로 같은 병기의 환자들 중에서도 예후는 다양하다는 보고가 많다. 그래서 유방암을 유전자의 형태에 따라서 4가지로 흔히 분류하여서 예후를 추정하는데 도움을받고 있다. 이 4가지 유형중에서 HER-2형은 ER(-), PR(-), HER(+)의 표현형을 보이며 예후에 대해서 다양한 보고가 있는 것으로 알려져 있다. 이에 본 조사는 본원의 환자를 대상으로 HER-2형의 세포유형이 예후에 어떤 영향을 미치는지를 알아보고자본 연구를 시작하였다.

방법: 2001년 1월부터 2005년 12월 까지 본원에서 유방암으로 수술을 한 822명의 환자를 대상으로 하였고 의무기록을 후향적으로조사하였다. 환자들은 수용체의 유무에 따라서Luminal A(ER(+), PR(+), HER-2(-)), Luminal B(ER(+), PR(+), HER-2(+)), HER-2(ER(-), PR(-), HER-2(+)), triple negative (ER(-), PR(-), HER-2(-))로 나누어서 각군을 비교분석 하였다. 임상 병리학적 인자를 중심으로 무병생존율에미친 영향과 전체생존율에 영향을 미친 인자를 분석하였다

결과: 환자의 평균 연령은 52세였으며 종양의 평균 지름은 2.53cm였다. 180명(25.5%)의 환자가 HER-2형태로 분류되었으며 157명(22.3%)의 환자가 luminal A로, 247명(35.0%)의 환자가 Luminal B 로 그리고 남은 121명(17.2%)의 환자가 triple negative type로 분류되었다. HER-2군 환자중 stage I환자가 다른 군에 비해서 적었으며(15.9%, p=0.006), stage III 환자가 다른 군에 비해서 많이 분포되어 있었다(56.6%, p=0.020). HER-2군 환자의 5년 무병생존율은 86.14%로 다른 군에 비해서 낮았다(p=0.0360). 또한 5년 전체생존율도 93.52%로 다른 군에 비해서 낮았다(p=0.0061). HER-2 groups환자에서 병기의 분포는 다른 그룹과 차이는 없었지만 triple negative groups에 비해서는 초기 유방암 환자의 비율이 높았다(p=0.006). 종양의 분화정도는 HER-2 group과triple negative group에서 분화도가 나빴다(p=0.020). HER-2 group의 무병생존율은 86.14%로 다른 그룹과 차이는 없었다(p=0.2544). HER-2 group의 전체생존율 또한 93.9%로 다른 그룹과의 차이는 없었다(p=0.3218).

결론: HER-2군의 환자의 무병생존율과 전체생존율이 다른환자군에 비해서 낮았으며 HER-2환자군에 trastuzumab으로 치료한 기간이 짧아서 trastuzumab의 치료효과를 평가하기에는 한계가 있는 것으로 생각된다. 향후 trastuzumab의 치료효과를 관찰하는 것이 환자들의 전체생존율의 향상에 도움이 될것으로 생각된다.

Key words : Breast carcinoma; HER-2, stage, DFS, OS

Introduction

Breast carcinomas have been traditionally classified as hormone receptor (ER and/or PR)-positive or negative.[14] In the recent years, newer approaches to breast carcinomas using gene-expression profiles and immunohistochemical (IHC) biomarkers have identified at least four subtypes of these tumors.[15] These subtypes are basal-like (ER-negative, PR-negative, HER2-negative), HER2-positive (ER-negative, PR-negative, HER2-positive), luminal A (ER-positive and/or PR-positive and HER2-negative), and luminal B (ER-positive and/or PR-positive and HER2-positive).[8] The human epidermal growth factor receptor type-2 (ERBB-2),

교신저자 : 이 충 한
주소 : 602-702 부산광역시 서구 암남동 34번지
고신대학교 복음병원 외과학교실
TEL : 051-990-6462
E-mail: lovebrest@naver.com

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generally referred to as ‘‘HER-2/neu’’ is known to be over-expressed in approximately 25–30% of breast cancers.[1] The c-erb-B 2/neu oncogene is localized on chromosome 17q11 and encodes a membrane receptor tyrosine kinase protein.[2] The HER-2 molecule is one of several growth factor receptors and is localized on the cell membrane where it plays important roles in the growth and proliferation of normal cells as well as cancer cells.[3] The prognosis of breast cancer patients showing over-expression of HER-2 is known to be significantly worse than that of patients with low HER-2 expression, and HER-2 status is thought to be an important prognostic factor of breast cancer.[4] HER2 overexpression is associated with increased tumor aggressiveness, increased rates of recurrence, and increased mortality in both node-positive and node-negative patients.[5,6] On the other hand, ER and PR are inversely related to HER2 overexpression, and the patients with ER-negative/PR-negative/HER2-positive tumor have a more aggressive clinical outcome.[7]The aim of this study was to determine the prognostic significance of HER-2 goupswith respect to disease-free survival (DFS) and overall survival (OS)in a group of homogeneously treated breast carcinoma patients.

Materials and methods

The medical records and the final pathological reports of female patients who underwent breast operation from 2001 to 2005 at Kosin University Gospel Hospital for primary invasive breast carcinoma within clinically operable stages were reviewed retrospectively. The follow-up cut-off date of this study was January 2008. Patient inclusion criteria for this study were as follows: no clinical features of locally advanced stage, no serious concomitant diseases, age less than 70 years, no prior specific treatment, having complete axillary dissection, having information on estrogen receptor status, progesterone receptor status and HER2 status, and having available adjuvant treatment if necessary, according to the current guidelines.[8,9] Eight hundreds twenty two patients met the eligibility criteria for the study.

Pathological lymph node classification and tumor staging were performedaccording to the American Joint Committee on Cancer criteria.[10,11] Histologic grading was performed using the criteria of Bloom and Richardson.[12,13]Lymphatic vascular invasion (LVI) was defined as the presence of tumor emboli in peritumoral lymphatic spaces, capillaries or postcapillary venules. ER status, PR status, p53 and HER2 status were determined by immunohistochemical means on paraffin-embedded tissue. ER status and PR status were taken as positive if more than 10% of tumor cells showed staining. Immunohistochemical score of 3+ for HER2 was accepted as HER2 positivity.

The primary outcome examined was DFS, and secondary endpoint of the study was overall survival (OS). For the estimations of DFS and OS as endpoint by the end of follow-up, the standardized definitions proposed recently by Hudis etwere used.[14] The first event approach was used for DFS estimates. DFS was estimated from the date of biopsy diagnosis before treatment to all types of first event as locoregional or distant metastasis, or all deaths due to breast carcinoma, new breast carcinoma or non-breast carcinoma asendpoint by the end of follow-up. Estimates of OS were evaluated from the date of biopsy diagnosis before treatment to the date of death due to breast carcinoma, new breast carcinoma or non-breast carcinoma related reasons by the end of follow-up.

Statistical tests were performed using the SPSS 12.0statistical software package for Windows (SPSS Inc, Chicago, IL). Survival estimates and curves were established using the Kaplan–Meier methodand differences in observed survival distribution among patient subgroups were tested with two-sided log-rank test. All survival rates were presented with their standard errors.

We used Pearson's correlation to determine the association of pairs of explanatory variables and differences in qualitative variables were evaluated by Chi-squared test, where necessary. All p-values were two-sided and a p-value of less than 0.05 was considered to indicate a statistically significant difference.

Table 1. patients and tumor characteristics and association with microarray

characteristics		Luminal A	Luminal B	HER-2	Basal	Total(n)	p-value
Age	>35	14(7.2)	15(5.0)	14(7.1)	10(7.6)	53(6.4)	0.661
	≤35	181(92.8)	283(95.0)	184(92.4)	121(92.4)	769(93.6)	
pT	1	72(40.7)	96(35.2)	54(30.5)	49(39.2)	271(36.0)	0.073
	2	90(50.8)	143(52.4)	102(57.6)	56(44.8)	271(36.0)	
	3	9(5.1)	23(8.4)	14(7.9)	16(12.0)	62(8.2)	
	4	9(0)	5(1.8)	6(3.4)	3(2.4)	14(1.8)	
pN	0	119(65.7)	149(52.8)	108(59.7)	68(54.8)	444(57.8)	0.177
	1	32(17.7)	57(20.2)	36(19.9)	27(21.8)	152(19.8)	
	2	14(7.7)	43(15.2)	15(8.3)	15(12.1)	87(11.3)	
	3	16(8.8)	33(11.7)	22(12.2)	14(11.3)	85(11.1)	
Stage	I	48(27.3)	54(19.6)	30(17.2)	33(27.0)	165(22.1)	0.008
	IIa	67(38.1)	90(32.6)	75(43.1)	34(27.9)	266(35.6)	
	IIb	17(9.7)	39(14.1)	26(14.9)	24(19.7)	106(14.2)	
	IIIa	15(8.5)	38(13.8)	7(4.0)	11(9.0)	71(9.5)	
	IIIb	1(0.6)	4(1.4)	4(2.3)	3(2.5)	12(1.6)	
	IIIc	13(7.4)	29(10.5)	23(13.2)	12(9.8)	77(10.3)	
	IV	4(2.3)	5(1.3)	3(1.7)	4(3.3)	16(2.1)	
Grade	G1	24(17.9)	27(13.6)	13(9.6)	9(9.7)	73(13.0)	0.012
	G2	54(40.3)	85(42.7)	44(32.6)	25(26.9)	208(37.1)	
	G3	56(41.8)	87(43.7)	77(57.0)	59(63.4)	279(49.7)	
P53	Negative	155(82.9)	173(61.3)	80(44.0)	63(50.4)	471(60.7)	0.0001
	Positive	32(17.1)	109(38.7)	102(56.0)	62(49.6)	30(39.3)	
Ki67	Negative	31(17.7)	27(10.0)	23(12.5)	25(20.2)	106(14.1)	0.020
	Positive	144(82.3)	243(90.0)	161(87.5)	99(79.8)	647(85.9)	

Results

The median age was 52 (range 26~70) years, median tumor size was 2.53 (range 2.6~9.4) cm, and the median number of lymph nodes in dissection materials was 18 (range 10–53). Patients' characteristics were given in Table 1. 180 patients (25.5%) were classified a HER-2, 157 patients (22.3%) were classified a Luminal A, 247 patients (35.0%) were classified a Luminal B, and Remaining 121 patients (17.2%) were defined as triple negative group. There is no distributional difference of age group distributions between four groups. The rate of patients with stage I was lower in HER-2 groups(15.9%, p=0.006) and that of patients with grade III was higher in HER-2 groups and triple negative groups(56.6%, 64.0%, p=0.020 respecitivley) and that of patients with p53mutation was higher in HER-2 and triple negative groups(54.5%, 54.4%, p=0.0001 respecitivley). The median observation time was 49 (range 26~94) months for patients still alive at the follow-up cut-off date. Whereas 82 patients (11.6%) had a distant metastasis. 26 patients (3.6%) died because of cancer-related reasons in their follow-up periods. The estimated 5-year DFS rate were 86.14% in HER-2 group and 87.96% in triple negative group . And the estimated 5-year overall survival rate was 93.52% for HER-2 group.

The univariate analysis for prognostic factors associated with DFS revealed that the tumor group as microarray was not statistically significant(p=0.2544)(Table 2). The Stage according to AJCC system is statically significant in DFS (p=0.0001). Also The univariate analysis for prognostic factors associated with OS revealed that the tumor group as microarray is not statistically significant(p=0.3218) (Table 3). In addition to the stage according to AJCC system is statically significant in OS(p=0.0001).

Discussion

Several studies demonstratedthat HER2-positive subtypes are correlated with reduced survival, and there is a considerable evidence at the molecular level that HER2 overexpression/amplification leads to up-regulation of

Table 2. five year disease free survival probabilities

Characteristics		N(events)	OS	p-value	N(events)	DFS	p-value
Type	luminalA	147(4)	97.28	0.0258	153(17)	88.89	0.1034
	luminalB	218(7)	96.79		239(22)	90.79	
	HER-2	151(11)	92.72		169(25)	85.21	
	Basal	11(0)	100		14(1)	92.86	
pT	1	222(9)	95.95	0.0063	241(21)	91.29	0.0001
	2	324(16)	95.06		359(42)	88.30	
	3	54(8)	84.91		61(18)	70.00	
	4	10(2)	80.00		10(6)	40.00	
pN	0	424(13)	96.93	0.0002	449(35)	92.20	0.0001
	1	125(4)	96.80		140(16)	88.57	
	2	66(6)	90.91		76(18)	76.32	
	3	66(12)	81.82		76(24)	68.42	
Stage	I	137(4)	97.08	0.0001	145(11)	92.41	0.0001
	IIa	228(9)	96.05		250(15)	94.00	
	IIb	94(2)	97.87		106(14)	86.79	
	IIIa	54(6)	88.89		62(16)	74.19	
	IIIb	8(2)	75.00		8(5)	37.50	
	IIIc	64(11)	82.81		72(21)	70.83	
	IV	11(2)	81.82		14(7)	50.00	
Grade	G1	64(1)	98.44	0.5841	67(2)	97.10	0.03020
	G2	160(6)	96.25		172(22)	87.21	
	G3	207(14)	93.24		231(25)	89.18	
ER	Negative	302(22)	92.72	0.5553	340(47)	86.18	0.5553
	Positive	327(10)	96.94		350(37)	89.43	
PR	Negative	340(24)	92.24	0.0421	379(57)	84.96	0.0691
	Positive	291(9)	96.91		312(28)	91.03	
P53	Negative	348(14)	95.98	0.8402	381(35)	90.81	0.7650
	Positive	235(11)	95.32		259(28)	89.19	
HER-2	Negative	226(11)	95.13	0.4846	246(28)	88.62	0.7139
	Positive	353(17)	95.18		392(42)	89.29	
Ki67	Negative	85(4)	95.29	0.3897	96(7)	92.71	0.1741
	Positive	493(20)	95.94		537(55)	89.76	

multiple secondary target molecules which affect the malignant phenotype.[16,17]The present study showed that HER2-positive tumors as apart from ER or PR status had a higher incidence of event and, therefore, these patients showed the poor survival rates, and HER2 status was an independent prognostic factor in the multivariate analysis, as similar to other studies.[18,19]HER2 is amplified and/or overexpressed in approximately 30% of breast carcinomas,6 as in our study. In spite of the large number of reports on the prognostic significance of c-erbB-2 in breast cancer, data on the association of c-erbB-2 expression with locoregional relapse has been scarce. Furthermore, c-erbB-2 overexpression is frequently detected in comedo type cancer in situ and other types showing necrosis, features that have been associated with an increased risk of breast recurrence. In the present study of patients with node-positive breast cancer, where most of the patients were treated by mastectomy, approximately half of the patients with locoregional recurrence had tumours showing overexpression of c-erbB-2. The rate of positivity among control patients (25%) is close to that found for node-positive breast cancer in most other studies. The odds ratio, comparing patients with and without relapse, increased significantly with the level of c-erbB-2 expression, and the significance remained in the multivariate analysis which incorporated number of lymph node metastases and other factors. Hormone receptor status, tumour size, DNA ploidy or S-phase fraction – all of which are known indicators of distant recurrence – were not of independent predictive value. The latter result is similar to that of another study of locoregional recurrence performed in patients treated by mastectomy, in which the degree of nodal involvement was found to be the only significant factor. The limited value of estrogen receptor status and

S-phase fraction34 for prediction of locoregional recurrence is consistent with the findings in other studies. Correlations between local spread, extension of in situ components and c-erbB-2 overexpression could possibly be related to factors acting on the c-erbB-2 receptor. In another study of node-negative breast cancer it was concluded that the association of c-erbB-2 overexpression with poor prognosis was confined to invasive tumours lacking an in situ component. Taken together, these studies indicate that interactions between c-erbB-2 expression and other factors may be important determinants of clinical outcome. There is a growing body of evidence suggesting that systemic therapy influences the relationship between c-erbB-2 expression and prognosis. In some studies where c-erbB-2 was found to be a significant indicator of poor survival, lymph node dissection was not performed in all patients and few received radiotherapy. Breast cancer survival following locoregional relapse was not significantly related to c-erbB-2 expression in the present study, although overexpression correlated with early locoregional recurrence. In a recent report, Arriagada and colleagues26 suggested that adequate locoregional treatment may prevent secondary dissemination in a subgroup of breast cancer patients. Among the patients who had a distant relapse as a second event in the present study, two-thirds showed c-erbB-2 overexpression in the primary tumor. In our series including patients treated homogeneously and adjuvant treatments, the rate of HER-2 type patients was 25.5%, which is similar to some reports but higher than others.[9,10] These previous reports indicated that HER-2 type tumors were associated with advanced stage and high grade, and therefore had a poorer outcome in terms of overall survival and disease-free interval. In our study, although more deaths were observed in HER-2 type patients than other type group patients, overall survival rates in these groups were statistically important. This result may be related with the relatively short follow-up period. On the other hand, more number of events was observed in the triple negative patients, and therefore, DFS in this group of patients was worse, in accordance with other studies.[19,20] In spite of this finding, the DFS for HER-2 subtype was statistically different from those for other subtypes.

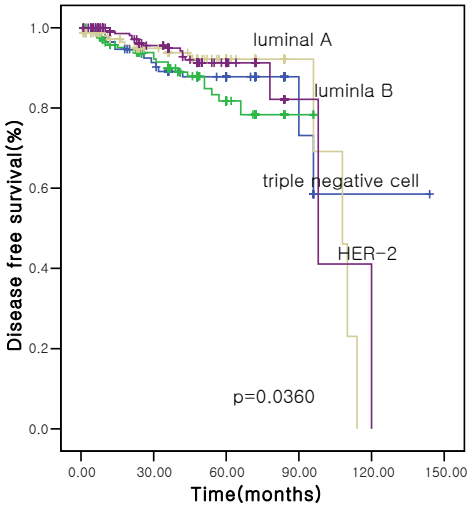

Fig 1. Disease free survival curves according to the patient's groups

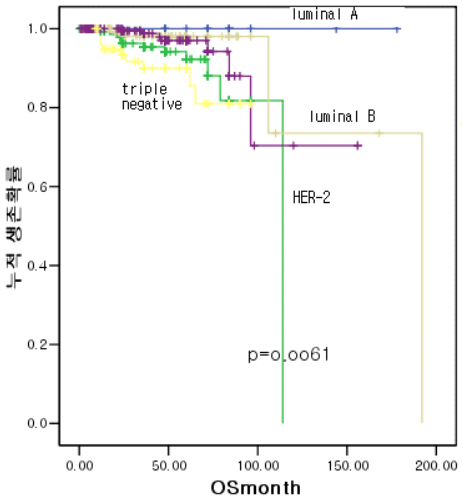

Fig 2. Overall survival curves according to the patient's groups

Conclusion

In conclusion, our study indicates that HER-2 type breast carcinoma is not uncommon and it tends to display a more aggressive clinical course, as triple negative breast carcinoma, and the tumor subtype as HER-2 type is an independent predictor of OS. In our series including patients treated homogeneously and adjuvant treatments, the rate of HER-2 type patients was 25.5%, which is similar to some reports but higher than others.[9,10] These previous reports indicated that HER-2 type tumors were associated with advanced stage and high grade, and therefore had a poorer

outcome in terms of overall survival and disease-free interval. In our study, although more deaths were observed in HER-2 type patients than other type group patients, overall survival rates in these groups were statistically important. Trastuzumab treatment strategies should be investigated for patients with HER-2 positive breast carcinoma. Further studies will be appropriate to confirm the validity of our results.

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