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HER-2 Status in Breast Cancer Patients with and Without Brain Metastases

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Abstract: Several retrospective studies have illustrated the correlation between HER2 overexpression and increased risk of metastatic disease and poor prognosis in breast cancer. In a retrospective study, we evaluated the risk of brain metastases in these patients. Medical charts of 155 patients with breast cancer were reviewed for IHC and HER2 status, sites of metastases, total dose and fraction size of radiotherapy for brain metastasis,age and coure of the disease. Sample size was determined by statistical analysis according to previos studies. We selected 20 patients with brain metastases as case and 60 patients without brain metastasis in control group. IHC reports was available for 80 patients. Eighty five percent (17/20) of patients with brain metastasis were HER2 positive compared with 40% (24/60) of HER-2 positivity in patients without brain metastases (with and without visceral metastasis) (p = 0.001). Concidering other metastatic sites, the probability of being HER2 positive was higher in patients with brain metastasis (with and without visceral metastasis) (85%, 17/20), compared with patients who had presented with visceral metastasis only (27.3%,3/11) (p = 0.004). Thirty six patients among 60 cases (60%) without brain metastases and 11 patients out of 20 cases with brain metastases (55%) were younger than 50 years old (p = 0.649).

Key words: Breast cancer, HER2, brain metastases

INTRODUCTION

Breast cancer is the most common malignancy in women in the United States and the second cause of cancer death after lung cancer (Jemal *et al*., 2006; EBCT, 2005). Central nervous system is one of the most important sites which is involved by metastatic breast cancer. Indeed breast cancer is the second most common cause of CNS metastases with an incidence estimated to be 10-16% in stage IV disease (Jemal *et al*., 2003). These figures underestimate the true incidence, given that brain metastases are found in 30% of patients at autopsy (Johnson and Young, 1996). It should be noted that CNS involvement due to metastatic breast cancer is associated with substantial morbidity and mortality. Several investigators have tried to define the role in of HER2 over-expression in CNS involvement by metastatic breast cancer. HER2 is one member of big family of epidermal growth factors which is amplified or over-expressed in 20-30% of invasive breast cancers and is associated with an aggressive course of disease, frequent disease recurrence and a shorter survival (Cooke *et al*., 2001).

However, there is limited data about association of HER2 overexpression and brain metastasis in breast cancer. For example among 319 women with primary breast cancer, HER2 overexpression was the strongest predictor of the site of first relapse in a multivariate model, with a 4.3% vs. 0.4% incidence of brain metastases (Lassman and De Angelis, 2003). As systemic therapy of metastatic breast cancer improves, CNS involvement is becoming a more widespread problem. The association of CNS metastases with HER2 overexpression merits special mention. In an attempted to further investigate the risk of brain metastases in patients with HER2 positive breast cancer, we conducted this retrospective analysis.

MATERIALS AND METHODS

Between January 2005 to March 2007, through a retrospective study, the medical charts of 155 patients with metastatic breast cancer, in Imam Hossein Medical Center, Tehran Iran, were reviewed for IHC and HER2 status, sites of metastases, total dose and fraction size of radiotherapy for brain metastasis, age and the course of

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disease. HER2/neu positive status was defined as IHC 3+ or FISH +. Sample size was determined by statistical analysis according to previous studies. We selected 20 patients with brain metastasis as the case and 60 patients without brain metastasis as the control group.

RESULTS

IHC reports was available for 80 patients. As the main finding, eighty five percent (17/20) of patients with brain metastasis were HER2 positive compared with 40% (24/60) of HER2 positive in patients without brain metastases (with and without visceral metastasis) ($p = 0.001$). Considering other metastatic sites, the probability of being HER2 positive was higher in patients with brain metastasis (with and without visceral metastasis) (85%, 17/20), compared with patients who had presented with visceral metastasis only (27.3%, 3/11)($p = 0.004$).

Forty one of the 80 patients (51.2%) were HER2 positive. Among HER2 negative patients metastases frequency (visceral, brain or both) were 28.2 % (11/39) but among HER2 positive were 48.8% (20/41) ($p = 0.059$). While only 3 out of 39 (7.7%) HER-2 negative patients developed brain metastasis, 17 out of 41(41.5%) HER-2 positive patients appeared it ($p = 0.001$). Thirty six patients among 60 cases (60%) without brain metastases and 11 patients out of 20 cases with brain metastases (55%) were younger than 50 years old ($p = 0.649$). Among 20 patients with brain metastasis, 12 patients received brain radiotherapy with more than 200 cG per fraction and total dose of 3000 cG, 5 patients with more than 3000 c cG G (less than 200 cG per fraction) and 3 patients brain were not treated with RT. Median survival were 6.5, 10.5 and 3 month, respectively.

DISCUSSION

Breast cancer is the second cause of cancer death and also the second most common cause of CNS metastatic involvement (Jemal *et al*., 2003, 2006; EBCT, 2005). In 1982 Amer for first time suggested that effective systemic chemotherapy may alter the natural history of breast cancer, leading to an increased risk of CNS metastases (Amer, 1982). Considering the substantial morbidity and mortality of brain metastasis, many investigators are concerned about the association between HER2 positivity and brain metastasis in patients with metastatic breast cancer.

HER2/neu over-expression or amplification is seen in up to 30% of cases of invasive breast cancer and is a prognostic factor for poor outcome and a predictive factor for response to treatment with anthracycline-based and taxane-based chemotherapy, hormonal therapy and also targeted therapy with trastuzumab in IHC3+ or FISH positive breast cancer (Paik *et al*., 1998; Thor *et al*., 1998; Pegram *et al*., 1998; Berry *et al*., 2000).

In a retrospective analysis Altaha *et al.* (2005) studied 110 patients with metastatic breast cancer and reviled that younger patients with HER2 positive status may have a higher risk for brain metastasis compared with older patients with negative HER2 (Altaha *et al*., 2005).In another study Crivellari *et al.* (2006) assessed HER2 over-expression in breast cancer patients developing brain metastasis after initial chemotherapy and found out that up to 62% of patients with brain metastasis were HER2 positive. However, in this study HER2 status was not evaluated in other patients without brain metastasis (Crivellari *et al*., 2006).

In our study, assessment of HER2 status in 80 patients with metastatic breast cancer, reviled a significant difference in HER2+prevalence between patients with brain metastasis compared with patient without CNS involvement (85 vs. 40% p;0.001).

Although the results need to confirmed in a large scale study, this finding may be very important, because it may justify an intensive and newer treatment approach such as targeted therapy in patient with early stage, HER2 positive breast cancer, to overcome this late complication.

Besides this considerable finding our study has some limitation such as; the impact of pre analytic issues including storage, duration and type of fixation, intensity of antigen retrieval, type of antibody (polyclonal versus monoclonal) and the nature of system control samples and, most importantly, the difficulties in applying a subjective slide scoring system.

CONCLUSION

This retrospective analysis suggest that HER2 positive status in patients with breast cancer may be associated with a higher risk of brain metastasis in the course of disease, however the risk of brain metastasis seems not to be different among younger and older patients.

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