Cukurova Medical Journal

Araştırma Makalesi / Research Article

Discordance Between HER-2/NEU Expression Assessed Using Immunohistochemistry (IHC) and Fluorescence in Situ Hybridization (FISH): Is It Important to Detect?

HER-2/NEU Ekspresyonun Saptanmasında İmmunohistokimyasal ve Fish Yöntemi Arasında Diskordansın Belirlenmesi Önemli midir?

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Cukurova Medical Journal 2014;39(1):53-60.

ABSTRACT

Purpose: Assessment of HER-2 has become of great importance following the advent of HER-2 antibody treatment. Use of trastuzumab therapy depends on the assessment of HER-2 via standard immunohistochemistry (IHC) assays for protein overexpression or via fluorescence in situ hybridization (FISH) for gene amplification. The aim of this study was to determine the rate of discordance between FISH and IHC in our hospital. The rate of discordance varies from hospital to hospital, and due to certain staff, technical, and biological reasons, IHC and FISH may not be concordant in every patient. It is important to determine the rate of discordance between these 2 methods and attempt to lower it. In addition to the rate of discordance, we also investigated the reasons for the discordance and what affect it has on the progression of the disease and treatment.

Material and Methods: A total of 79 patients with breast cancer were assessed for HER-2 protein expression via IHC and HER-2 gene amplification via FISH.

Results: Among these 79 patients, 47 (59.5%) were FISH (–) and 32 (40.5%) were FISH (+), whereas FISH was negative in 8 (10.4%) patients that were HER-2 (3+) and FISH was positive in 9 (11.4%) patients that were HER-2 (1+). The discordance rate was 21.5%.

Conclusion: The clinical implication of this discordance rate and it's affect on the choice of appropriate therapy are of critical importance. As such, it would be beneficial for each hospital to determine its own discordance rate.

Key Words: Breast cancer; HER-2/neu; IHC; FISH; discordance rate

ÖZET

Amaç: HER-2'nin değerlendirilmesi, HER-2 antikor tedavisinin takibinde büyük öneme sahiptir. Transtuzumab tedavisinde HER-2'nin değerlendirilmesi protein aşırı üretiminin standart immünohistokimyasal yöntemler ile veya gen amplifikasyonunun FISH yöntemi ile belirlenmesine bağlıdır. Bu çalışmanın amacı hastanemizde kullanılan bu iki yöntem arasındaki diskordans oranını incelemektir. Diskordans oranı hastaneler arasında farklılık göstermektedir, bu farklılık çalışanlara, teknik nedenlere ve biyolojik nedenlere bağlı olabilmektedir. Dolayısıyla bu iki metod arasındaki diskordans oranını belirlemek ve bu oranı minimize önemlidir. Bunlara ek olarak, diskordansın sebeplerini, hastalığın ve tedavinin progresyonu üzerine nasıl etki ettiğini araştırdık.

Materyal ve Metod: Meme kanseri tanısı alan toplam 79 hastada HER-2 protein ekspresyonu immunohistokimyasal, HER-2 gen amplifikasyonu ise FISH yöntemleriyle incelendi.

Bulgular: İncelenen 79 hastadan 47 sinde (%59.5) FISH (-) 32 sinde (%40.5) FISH (+), öte yandan FISH negatif olan 8 (%10.4) hasta için HER-2 (3+) ve FISH pozitif 9 hasta (%11.4) içinde HER-2 (1+) bulundu. Diskordans oranı %21.5 tir.
Sonuç: Diskordans oranının klinik implikasyonu uygun tedavi prosedürünü seçmek için önemlidir, bu yaklaşım hastanelerin kendi diskordans oranlarını belirlemeleri için faydalı olabilir.
Anahtar Kelimeler: Göğüs kanseri; HER-2/neu; IHC; FISH; diskordans oranı

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INTRODUCTION

HER-2 molecule is a 185-kDa membrane receptor with tyrosine kinase activity[1]. HER-2 is routinely evaluated in all cases of invasive breast cancer to aid in determining the appropriate treatment for early and metastatic breast cancers[2]. Since 2001, the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the National Academy of Clinical Biochemistry have suggested routine evaluation of HER-2 expression, both in newly diagnosed and metastatic breast cancer patents[3-5].

HER-2 overexpression is seen in 15-25% of breast cancer patients and is usually accompanied by HER-2 gene amplification[6-8]. As trastuzumab has a therapeutic effect only on breast cancers associated with HER-2 overexpression or HER-2 gene amplification[10], evaluation of HER-2 has increased in importance with the availability of trastuzumab, which is an anti-HER-2 monoclonal antibody that binds to the extracellular domain of HER-2 in breast cancers[9]. Evaluation of HER-2 is not only used to determine the response to trastuzumab, but also predictive for response many systemic therapies[11] and resistance to endocrine therapy[12].

The prognostic value of HER-2 in breast cancer is controversial. In most, but not all studies it has been shown that HER-2 overexpression in the primary tumor determined using IHC is associated with a poor prognosis in untreated patients[1,13-15]. In some studies HER-2 overexpression is associated with a poor prognosis when other factors associated with a poor prognosis are present[16]. ASCO does not recommend HER-2 assesment alone as a prognostic factor[3].

Although a number of methods are used to evaluate HER-2, IHC and FISH are the most commonly used[6]. Immunohistochemically determined HER-2 overexpression is a good indicator of the clinical benefit of trastuzumab[7]. A score of 0-3 is made according to IHC staining; a score of 0-1+ is considered negative and 3+ is considered positive, whereas a score of 2+ requires evaluation of HER-2 gene amplification via FISH[2]. Gene amplification is identified via the FISH method in 24% of tumors with a HER-2 score of 2+ based on IHC.

Some studies have reported discordance between IHC and FISH. Although the biological basis of this discordance is unclear, it could be multifactorial because of the mutations in the genes that control HER-2 expression[6]. This discordance may lead to inadequate or unnecessary treatment; therefore, each hospital should evaluate its patients in consideration of its discordance rate, and those with a discordance rate above the expected level should review their methods.

MATERIALS and METHODS

Patient characteristics

The present study included 79 patients diagnosed with breast carcinoma that were referred to Cukurova University, Medical Faculty, Medical Oncology Department between 2005 and 2010. Inclusion criteria were as follows: histopathologically confirmed invasive breast carcinoma, estrogen and progesterone receptors in the tumor tissue, and axillary lymph node involvement. All of the patients were staged in accordance with the American Joint Committee on Cancer (AJCC) Tumor Node Metastasis (TNM) System. Each patient's paraffin block was

examined for HER-2 expression using the IHC method and for HER-2 gene amplification using the FISH method. The assessment of HER-2 expression via the IHC method was performed by 1 pathologist and was scored as 0-3 according to staining characteristics using the Hercep Test™. PathVysion HER-2/neu FISH kits were used for all patients at the same hospital and the results were denoted as positive or negative. All the patients were evaluated in terms of their ongoing treatment. The patients were divided into groups according to IHC HER-2 score of 0-3+, and FISH (+) and (–).

Statistical methods

Data obtained in the study were analyzed based on appropriate tests using SPSS v.14.0.

RESULTS

Mean age of the patients was 45 years (range: 24-75 years). In all, 3 (3.8%) of the patients were stage I, whereas 47 (59.5%) were stage II, 15 (19%) were stage III, and 14 (17.2%) were stage IV. ER was negative (ER–) in 25 (31.4%) of the patients and positive (ER+) in 54 (68.4%). PR was negative (PR–) in 28 (35.4%) of the patients and positive (PR+) in 51 (64.6%). No axillary lymph node involvement was observed in 25 (35.4%) of the patients, whereas 51 (64.6%) patients had axillary lymph node involvement. FISH was negative in 28 (35.4%) and positive in 21 (42.9%) of the patients without axillary lymph node involvement, whereas it was negative in 19 (24.1%) and positive in 11 (36.7%) of the patients that had axillary lymph node involvement. IHC HER-2 was 1+ in 19 (24.1%), 2+ in 17 (21.5%), and 3+ in 13 (16.5%) of the patients without axillary lymph node involvement, versus 1+ in 9 (11.4%), 2+ in 11(13.9%), and 3+ in 10 (12.7%) of the patients with axillary lymph node involvement.

FISH was negative in 19 (24.1%) and positive in 9 (11.4%) of the 28 (35.4%) patients with an IHC HER-2 score of 1+, whereas it was negative in 20 (25.3%) and positive in 8 (10.1%) of the 28 (35.4%) patients with an IHC HER-2 score of 2+, and negative in 8 (10.1%) and positive in 15 (29.1%) of the 23 (29.1%) patients with an IHC HER-2 score of 3+. Overall, 32 (40.5%) patients were FISH (+) and 47 (59.5%) patients were FISH (–) (Table 1). The discordance rate was 21.5%. Among the patients, 32 received trastuzumab therapy, of which 3 developed a brain metastasis and had trastuzumab therapy replaced by lapatinib.

DISCUSSION

HER-2 protein overexpression, which is usually the result of HER-2 gene amplification, causes progression of breast tumors by means of strengthening cell proliferation and adhesion, affecting mortality and recurrence[17]. HER-2 gene amplification is associated with a more aggressive course, as well as an increase in the risk of recurrences and a decrease in disease-free and overall survival[17-20].

In 2 randomized studies , compared to chemotherapy alone, addition of trastuzumab to chemotherapy regimens improved survival in metastatic patients with HER-2 protein overexpression and HER-2 gene amplification[21,22]. Adding trastuzumab to adjuvant chemotherapy regimens improves disease-free and overall survival[23-27]. HER-2 positivity plays a determinative role in the response to chemotherapy regimens, including anthracycline and taxane. As such, precise assessment of HER-2 has become crucial with the advent of trastuzumab, an anti-HER-2 monoclonal antibody that binds to the extracellular domain of HER-2[9].

Although IHC is an easier and less expensive method than FISH, it is difficult to standardize. FISH, on the other hand, is more sensitive and specific, but is more expensive. The FISH method is 4-fold more expensive than IHC, and requires more expertise for its application and evaluation[28]; therefore, various studies have been conducted to compare local laboratories with central laboratories. In a study performed by the National

Surgical Adjuvant Breast and Bowel Project (NSABP-31), a discordance rate of 19% was noted when HER-2 assessed via the IHC method in a small laboratory was re-evaluated in a central laboratory[29]; the rate was 21.5% in the present study. This rate decreased to 4% when evaluated in a larger laboratory. The present study shows that HER-2 should be evaluated in a well establihed laboratory or in a laboratory in which FISH is available. In the present study any laboratory in which >100 HER-2 evaluations are made annually was defined as a large laboratory[29]. HER-2 evaluation guidelines in England define large laboratories as those at which at least 250 HER-2 evaluations are made annually via IHC and at least 100 HER-2 evaluations are made annually via FISH[28], which we think is a more realistic approach.

This discordance between local and central laboratories has led to a gradual increase in interest in primary use of the FISH method among oncologists and pathologists in the USA[30]. O'Malley et al. studied HER-2 assessment via IHC and FISH in local and central laboratories using 4 methods. They associated the observed discordance between the local and central evaluation of HER-2 to the scoring method as well. It was observed that the rate was 10.3% when the Hercep Test™ and Allred scoring system were used, whereas it reached 20.7% when the DAKO scoring system was used. In contrast, the discordance rate was 5.2% when the Allred scoring system was used in cases that were Hercep Test™ (–), whereas 100% discordance was observed with the DAKO scoring system[30]. It was expected that the criteria for HER-2 positivity (intense membrane staining in uniform invasive tumor cells >30%)[2] via re-evaluated IHC would lower the false positivity rate[30]. ASCO/CAP guidelines recommend verification via the FISH method in cases of strong invasive tumors in which complete membrane staining is between 10% and 30%, or in weak cases in which membrane staining is >10%[2].

Despite the high correlation between FISH in the cases that were HER-2 (3+) based on IHC, amplification might not be observed via FISH in some cases that are HER-2 (3+) based on IHC. Although biological basis of this discordance is unclear, it might be multi-factorial due to mutations, including those in the genes that are responsible for HER/2neu expression. Aneuploidy in chromosome 17 might explain the inability to observe amplification in some cases that are HER-2 (2+) or (3+) based on IHC[6,31]. This raises the possibility that HER-2 (2+) or (3+) cases in which amplification cannot be observed via FISH should be confirmed by another method[1]. Recently, it was shown that the X-linked FOXP3 (forkhead box P3) gene controls HER-2/neu protein expression. FOXP3 is a breast cancer suppressor with an X-linked inheritance pattern, which is an important suppressor of the ERBB2/HER-2 oncogene. FOXP3 suppresses tumor enlargement, despite overexpression of ERBB2/HER-2[31]. The other important point is that although the staining pattern via IHC is defined in some studies as dark and circumferential only, it has been reported that granular or linear staining is more important. Some studies suggest that a granular staining pattern via IHC is more common in patients that are HER-2/neu (3+) and FISH (–), and cases that exhibit such staining pattern should be considered 2+ instead of 3+[32,33].

In the present study, although it was expected to be (–), positivity was noted with FISH in 9 (11.4%) of the 28 patients that had 1+ staining via IHC. This might have been due to the above-mentioned reasons, except for the technical factors. Whereas these 9 patients were not considered candidates for lapatinib therapy following trastuzumab therapy when they were evaluated with IHC only, they were based on FISH assessment. Despite the fact that FISH is an expensive method, anti-HER-2 therapies further increase the cost of treatment. Accurate decision-making is of critical importance for both treatment outcome and cost.

The prognostic value of HER-2 remains controversial. Most studies reported that HER-2 expression in tumor tissue based on IHC is associated with a poor prognosis[1,13-15]. Other studies reported that HER-2 overexpression, in association with tumor grade, size, and nodal status, is associated with a poor prognosis[16]. HER-2 overexpression is associated with a poor prognosis in patients with a positive node[8,34-36]. Studies that included patients with early-stage disease reported that the prognostic value of HER-2 was unclear in untreated patients with a negative node. In contrast, a recent study that included 2026 breast cancer patients (76% were untreated) reported that HER-2 overexpression was observed via IHC, and that those that were IHC 2+ were confirmed via FISH. Additionally, 10-year recurrence-free survival (65.9% vs. 75.5%; P = 0.01) and breast cancer-specific survival (75.5% vs. 86.3%; P = 0.001) rates were lower in those with HER-2 overexpression[37].

In the present study 90% of the study population were node negative patients with tumors >1 cm, which confirms that the use of trastuzumab in those patients was the correct choice. The results show that HER-2 overexpression was correlated with a poor prognosis in node-negative and node-positive early-stage breast cancer patients. Based on the International Consensus Group scoring system, in the presence of HER-2 overexpression chemotherapy should be initiated[38]. As such, accurate determination of HER-2 expression is of critical importance to the prognosis and choice of therapy.

Trastuzumab therapy costs more than US$100,000 per breast cancer patient and fatal cardiotoxicity is a well known side effect of this treatment[39]; therefore, accurate decision-making is a critical issue. Although standards for HER-2 evaluation are clear, according to ASCO/CAP guidelines, different criteria are likely to become important in the further. As an alternative to the standard IHC and FISH methods, LightCycler monoplex polymerase chain reaction[8] is currently generating interest.

As there are no national guidelines for the evaluation of HER-2 overexpression in Turkey, it is evaluated in accordance with international guidelines. No specific definition of local/central laboratory has been made in Turkey; therefore, discordance between local and central laboratories has not been examined in Turkey. The discordance rate between IHC and FISH changes from hospital to hospital due to certain underlying personal and technical causes. It is necessary to determine and lower the rate of discordance between the 2 methods. The discordance rate was 21.5% at the hospital at which the present study was conducted. This rate was considered high for this hospital, which performs 90 FISH analyses annually; however, as the number of patients in the present study was limited, we think that studies that include more patients are needed for more precise evaluation. Discordance generally varies between 4% and 9%[29]. Although immunohistochemical examination is used at many laboratories, FISH is performed only at large laboratories. Both IHC and FISH are used at our hospital. To determine the rate of discordance between IHC and FISH in our patients the pre-existing data may be reassessed at a central laboratory. If a technical reason for the observed discordance cannot be determined, a biological factor may be responsible (aneuploidy, polysomy, etc.).

The present study's results highlight the importance of the clinical ramifications (choice of therapy, cost, etc.) of the discordance observed in the laboratory, and indicate that each hospital should determine its own discordance rate. Biological factors as well as technical factors should also be taken into consideration.

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geliş tarihi/received :12.08.2013
kabul tarihi/accepted:16.09.2013