Predictive value of HER-2 in breast cancer: Endocrine therapy

INTRODUCTION

Human epidermal growth factor 2 (HER-2) belongs to a four-member family of human epidermal growth factor receptors. They bind growth factors as dimers and transmit cellular signals. HER-2 consists of an extracellular domain for ligand binding, transmembrane part and intracellular domain with tyrosine kinase activity. Although HER-2 specific ligand has not been recognized yet, HER-2 is a preferred heterodimeric partner; HER-2 containing heterodimers are long-lived and their signals are relatively potent (1). HER-2 protein is encoded by c-erbB-2 gene located on the chromosome 17 and its amplification ultimately results in HER-2 protein overexpression.

HER-2 overexpression is present in about 60% of ductal carcinoma in situ (DCIS) and up to 30% of invasive breast cancer. Recent report confirmed that the HER-2 positive primary tumors remained HER-2 overexpressors during the metastasizing process, and there is no need for routine determination of HER-2 on metastatic sites (3). Gene amplification is usually determined by fluorescence in situ hybridization (FISH) method and HER-2 protein expression by immunohistochemistry (IHC) method.

The value of HER-2 overexpression as a poor prognostic marker in breast cancer seems to be well established (2,4). The predictive value of HER-2 overexpression was established only for trastuzumab (Herceptin, Hoffmann-LaRoche), monoclonal antibody that binds selectively to the external domain of HER-2 (2). However, the predictive value of HER-2 for endocrine therapy, such as tamoxifen (TAM) and aromatase inhibitors, and chemotherapy, such as anthracycline and non-anthracycline - containing regimens (CMF and taxanes) is still to be established.

HER-2 STATUS AND RESPONSE TO TAMOXIFEN

Estrogen receptor (ER) and progesterone receptor (PR) are the best predictive markers which help to select breast cancer patients whose tumors are most likely to respond to endocrine therapy. This means that the chance of response is the highest in an ER+/PR+ patient group and the lowest in ER-/PR- group (4). Interestingly, response to hormone therapy was noticed in about 10% of "double negative" breast cancer tumors. When those tumors are accompanied with HER-2+ phenotype, the chance for response to endocrine therapy almost reaches zero value, which is quite expectable. The more important question is whether HER-2 overexpression lowers the chance for response to endocrine therapy of steroid receptor positive (SR+) tumors.

Among all endocrine agents, TAM was the most frequently examined agent in both adjuvant and metastatic settings. At least seven studies thus far suggested that HER-2+ tumors were less likely to respond to TAM (Table 1).

Table 1. Clinical studies of HER-2 as a predictor of resistance to tamoxifen

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of pts</th>
<th>HER-2 assay</th>
<th>HER-2+ pts (%)</th>
<th>SR+ pts (%)</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carmanenigo C*</td>
<td>135</td>
<td>IHC</td>
<td>30</td>
<td>65</td>
<td>Adjuvant</td>
</tr>
<tr>
<td>Sjogren S*</td>
<td>47</td>
<td>IHC</td>
<td>21</td>
<td>85</td>
<td>Adjuvant</td>
</tr>
<tr>
<td>Stall*</td>
<td>519</td>
<td>IHC</td>
<td>NR</td>
<td>NR</td>
<td>Adjuvant</td>
</tr>
<tr>
<td>Nicholson R*</td>
<td>105</td>
<td>IHC</td>
<td>26</td>
<td>NR</td>
<td>Metastatic</td>
</tr>
<tr>
<td>Wright C*</td>
<td>65</td>
<td>IHC</td>
<td>22</td>
<td>46</td>
<td>Metastatic</td>
</tr>
<tr>
<td>Newsby J*</td>
<td>36</td>
<td>IHC</td>
<td>13</td>
<td>ER 53</td>
<td>Metastatic</td>
</tr>
<tr>
<td>Plunkett T*</td>
<td>241</td>
<td>IHC</td>
<td>31</td>
<td>NR*</td>
<td>Metastatic</td>
</tr>
</tbody>
</table>

Table 2. Studies of HER-2 status not found to be predictive of tamoxifen resistance

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of patients</th>
<th>HER-2 assay</th>
<th>HER-2+ Pts (%)</th>
<th>SR+ Pts (%)</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ravdin P12</td>
<td>595</td>
<td>IHC</td>
<td>16</td>
<td>100</td>
<td>Adjuvant</td>
</tr>
<tr>
<td>Knoop A13</td>
<td>high risk*</td>
<td>Streptavidin</td>
<td>18</td>
<td>PR 43</td>
<td>Adjuvant</td>
</tr>
<tr>
<td>Berry D*</td>
<td>651</td>
<td>IHC</td>
<td>24</td>
<td>100</td>
<td>Adjuvant</td>
</tr>
<tr>
<td>Love R*</td>
<td>470**</td>
<td>PCR</td>
<td>12</td>
<td>(ER 66)</td>
<td>Adjuvant</td>
</tr>
<tr>
<td>Archer S*</td>
<td>92</td>
<td>IHC</td>
<td>26</td>
<td>NR</td>
<td>Metastatic</td>
</tr>
<tr>
<td>Elledge R17</td>
<td>205</td>
<td>IHC</td>
<td>30</td>
<td>100</td>
<td>Metastatic</td>
</tr>
</tbody>
</table>

GUN-1 (Gruppo Universitario Napolitano) trial was the first adjuvant study that reported on resistance to TAM in HER-2+, node-negative (N-) patients after a median follow up of 12 years (5). On the contrary, Sjogren et al. (6) found that HER-2 overexpression is a predictor of TAM failure only in node positive (N+) patients (n=96), while this could not be confirmed for N-patients (n=202). Stall et al. (7) reported the results of 512 SR+ patients randomized to 2 years versus 5 years adjuvant TAM. Disease free survival (DFS) was significantly higher in 5-year treatment group in comparison to 2-year group. However, the relative risk for relapse for the 5-year group vs. 2-year group was 0.64 for those with no HER-2 overexpression, in contrast of 3.0 for HER-2 overexpressors, which does not reach statistical significance but do suggest a strong trend.

The predictive value of one marker could be more directly determined in metastatic setting because response rate (RR) is more reliable measure of sensitivity or resistance to given therapy than DFS and/or overall survival (OS) are in adjuvant setting. Nicholson et al. (8) found that, although HER-2 positive status confers low response to TAM +/- LH-RH agonist in peri/post-menopausal patients but does not further contribute to hormone insensitivity in epidermal growth factor receptor (EGFR) positive patients. In three reported studies (9,8,10) there was a small percentage of premenopausal patients...
treated with ovarian ablation, but these data were not separately reported from the postmenopausal treated with TAM. Newby et al. (11) also examined the level of expression of HER-2 before and after TAM therapy in a group of 36 patients with de novo or acquired TAM resistance. They did not notice the significant change in expression of either EGFR or HER-2 at relapse, so the acquired EGFR+ and/or HER-2+ positive phenotype was excluded as a reason of the development of TAM resistance.

There are several proposed mechanisms for resistance of SR+/HER-2+ breast carcinomas to TAM (1,5,11): a) decreased drug uptake within the tumor cell or increased its efflux; b) mutually negative feedback signaling loop between HER-2 and SR expression (estrogen-induced transcriptional inhibition of HER-2) was confirmed in preclinical studies, which might be partially inhibited by antiestrogen; the transfection of c-erb B2 gene of MCF7 cells, which are SR+ and sensitive to TAM, or its exposure to heregulin can result in down regulation of ER; c) the activation of ER tyrosine phosphorylation by growth-factor signalling pathways which results in estrogen independence.

In contrast to above-mentioned evidences, there are several clinical trials, which did not find such relation between HER-2 overexpression and failure to TAM. Radvan et al. (12) analyzed HER-2 status in almost 600 SR+, N+, postmenopausal women treated either with adjuvantCAF chemotherapy plus TAM, or TAM alone. They did not confirm that CAF chemotherapy further contributes to the benefit of TAM alone. Danish trial compared adjuvant TAM vs. no therapy in high-risk postmenopausal women after radical mastectomy and postoperative radiotherapy (13). At a median of 10 years follow-up the multivariate analysis did not confirm an increased risk for the recurrence after TAM treatment in HER-2+ patients, neither this was confirmed in ER-/HER2+ (11%). Cancer and Leukemia Group B study 8541 (CALGB) (14) investigated the effectiveness of three different dose schedules of adjuvantCAF chemotherapy followed by TAM in N+, ER+ breast cancer patients. There was no significant risk for either disease recurrence or death in ER+/HER2+ patients (24%) receiving TAM, in comparison to HER2- group. Love et al. (15) reported results of the randomized study of premenopausal women referred to adjuvant oophorectomy and TAM or no therapy. After a median follow-up of 3.6 years, they found a greater benefit from adjuvant therapy in HER2+ than in HER2- patients.

Two other studies also could not confirm that HER-2 overexpression is a marker of the resistance to TAM in locally advanced or metastatic breast cancer patients (16,17). The study of Elledge et al. (17) is particularly important because all included patients were ER+ and not previously treated for metastatic disease, majority of whom was postmenopausal and all of them were treated with TAM. There was no difference in RR, TTF and OS between HER-2+ and HER-2- subgroup.

Excluding the statistical issues and the differences in HER-2 assays, the conflicting results of these studies, concerning TAM resistance in HER-2+ patients, could be partially explained by various percentages of SR+ patients among included women.

HER-2 STATUS AND RESPONSE TO ENDOCRINE THERAPY OTHER THAN TAMOXIFEN

Lipton et al. (18) reported that elevated serum levels of ectodermal domain of HER-2 is significantly associated with lower RR, TTP and OS in SR+ metastatic breast cancer patients treated with second-line megestrol acetate or aromatase inhibitors (fadorozole or letrozole). Yamauchi et al. (19) also reported on the lower RR of HER2+ metastatic breast cancer treated with antiestrogen droloxifene, introduced as a first-line endocrine therapy for the metastatic disease. The most exciting are the results of the recently reported study on comparison of neo-adjuvant TAM vs. Letrozole, in 237 SR+ postmenopausal women (20). The IHC analysis of EGFR and HER-2 revealed that the RR to letrozole was superior to TAM in SR+/EGFR+ and/or HER2+ patients (15/17 vs. 4/19 patients, respectively, p=0.0004). The authors therefore concluded that the influence of EGFR and HER-2 on ER signaling pathway is ligand dependent, which could be prevented by full estrogen deprivation induced by intratumoral aromatase inhibition.

CURRENT RECOMMENDATIONS

Because of many biases that burden all studies, investigating the predictive role of HER-2 overexpression for the response to endocrine therapy, none of the currently available guidelines (Use of Tumor Markers in Breast and Colorectal Cancer: Clinical Practice Guidelines of the American Society of Clinical Oncology, 2000 NIH Consensus Statement on Adjuvant Therapy for Breast Cancer, 2001 St. Gallen International conference on adjuvant therapy of primary breast cancer, 2001 National Comprehensive Cancer Network, 2002 ESMO Minimum Clinical Recommendations) recommend the routine use of HER2 status in decision making process. However, further extensive investigation is strongly suggested.

Acknowledgement:

This work was supported by grant provided by the Ministry of Sciences, Technology and Development of Serbia, "Molecular biomarkers of estrogen (in)dependent breast cancer: biological and clinical aspects", No 1598.

REFERENCES

Predictive value of HER-2 in breast cancer: Chemotherapy

KEYWORDS: Breast Neoplasms, Receptor, erbB-2

Factors predicting response to chemotherapy can assist the clinician in selecting the right patients for chemotherapy and save the remaining patients from experiencing unnecessary toxicity. Additionally, such factors might also help in selecting the best possible regimen among the various cytotoxic agents for individual patients.

Today there are growing data indicating that HER-2 (p-erbB-2) could be helpful predictive marker in selecting the optimal chemotherapy regimen.

HER-2 STATUS AND RESPONSE TO ANTHRACYLINE-BASED CHEMOTHERAPY

A few studies providing level of evidence 2 have assessed the value of HER-2 as a predictive marker for the efficacy of anthracycline-based chemotherapy in breast cancer. A Cancer and Leukemia Group B (CALGB 8541) study analyzed 397 node-positive patients comparing three different dosages of a doxorubicin-based regimen (1). Patients were randomly assigned to receive cyclophosphamide, doxorubicin and fluorouracil (CAF) at one of the three levels of dose-intensity/cumulative dose: 600/600 mg/m² x 4 (“high dose”), 400/400/400 mg/m² x 4 (“moderate dose”) or 300/300/300 mg/m² x 4 (“low dose”). At a median follow-up of three years, it was found that in women who had HER-2 overexpressing tumors, disease-free survival (DFS) and overall survival (OS) were markedly improved in the “high dose” group, while in those patients classified as HER-2 low, no dose-response effect was seen. The authors concluded that HER-2 overexpression might be a marker of potential benefit from “high” doses of adjuvant chemotherapy.

The CALGB subsequently conducted an identical analysis in an additional cohort of 595 patients and the updated analyses of all available patients confirmed the dose-response effect in the HER-2 positive patients. The updated comparison of HER-2 positive and HER-2 negative patients who received the “high dose” CAF showed that the eight-year DFS and OS of HER-2 high group (69% and 78%, respectively) remained higher than those of HER-2 low group (55% and 65%), but these differences still did not reach statistical significance (2).

The question of whether there is a specific interaction between the efficacy of doxorubicin and HER-2 overexpression was addressed also in NSABP B-11 study (3). The patients were randomly assigned to receive either a combination of melphalan and 5-fluorouracil (PF) or a combination of melphalan, 5-fluorouracil and doxorubicin (PAF). The results showed a clear benefit from