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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 (c-erbB-2) could be helpful predictive marker in selecting the optimal chemotherapy regimen.

HER-2 STATUS AND RESPONSE TO ANTHRACYCLINE-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: 600/60/600 mg/m^2 x 4 ("high dose"), 400/40/400 mg/m^2 x 6 ("moderate dose") or 300/30/300 mg/m^2 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

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The manuscript was received: 03. 10. 2002.

Accepted for publication: 10.10.2002.

the addition of doxorubicin to PF combination in patients with overexpressed HER-2 (10-year DFS 39% vs. 24%, p=0.001), while no benefit was evident in patients with normal HER-2 expression (10 year DFS 36% vs. 40%, p=0.74).

Another NSABP study, B-15, showed similar but less statistically significant results in comparison to the B-11 study. In the B-15 study (4), patients with positive axillary lymph nodes were randomly assigned to receive doxorubicin and cyclophosphamide (AC), CMF or AC followed by CMF. It was shown that AC was superior to CMF in HER-2 positive patients only, although differences in outcomes did not reach statistical significance. The results indicate a preference for AC regimen in patients with HER-2 positive tumors, while both AC and CMF regimens may be considered for patients with HER-2 negative tumors.

European Organization for Research and Treatment of Cancer (EORTC) Trial 10854 compared the value of a single cycle of perioperative fluorouracil, doxorubicin and cyclophosphamide (FAC) to no further therapy (5). In this study, HER-2 expression was determined in 441 patients. The results suggested the reduced hazard of relapse in patients with HER-2 overexpressing tumors.

At the 2002 Annual Meeting of the American Society of Clinical Oncology (ASCO), the National Cancer Institute of Canada Clinical Trials Group presented data about the effects of HER-2 overexpression in previously published randomized trial comparing CMF to CEF as adjuvant therapy for premenopausal woman with axillary node-positive breast cancer. The data showed that women whose tumors had HER-2 overexpression obtained more differential benefit from CEF in comparison to CMF than women whose tumors did not show HER-2 overexpression (6).

Some smaller studies have also referred this issue. A Spanish study that compared CMF with FAC suggested that FAC was superior to CMF in patients whose tumors overexpressed HER-2 but equivalent in patients whose tumors did not overexpress the oncogene (7). An Italian study with 266 patients randomly assigned to receive either CMF or single-agent epirubicin also suggested a trend toward epirubicin being more effective then CMF in patients whose tumors overexpressed HER-2 (8). A German study with 144 patients randomly assigned to receive either high-intensity or a more standard epirubicin suggested that only in the non-overexpressing subgroup was there a benefit for the dose-intense regimen (9).

The possible predictive value of HER-2 overexpression of sensitivity to anthracyclines in the clinical investigations, could not be confirmed in the laboratory. Pegram et al. (10) transfected four breast cancer cell lines with HER-2 and than exposed them to doxorubicin. No alteration in chemosensitivity was observed in any of the transfected cell lines compared with the parent cell lines. These *in vitro* observations put under the question a direct role of HER-2 amplification in anthracycline sensitivity. As topoisomerase II-α is geographically located close to neu/erbB-2 on the same gene, some authors theorize that topoismomerase II-α may be the real predictive marker. Meta-analysis of HER-2 and topoisomerase II-α in a number of large randomized trials comparing anthracycline-containing to nonathracycline regimens may further clarify this question (6).

HER-2 STATUS AND RESPONSE TO NON-ANTHRACYCLINE CHEMOTHERAPY (CMF-LIKE)

While retrospective studies have pointed to the importance of HER-2 overexpression as a potential indicator of responsiveness to doxorubicin, the prediction of the response to cyclophosphamide, methotrexate and fluorouracil (CMF) has been more controversial.

Early studies suggested that HER-2 positive tumors do not benefit from CMF-based chemotherapy that, by contrast, has a considerable effect in tumors with no or minimal expression of this oncogene.

Gusterson et al. (11) demonstrated that in node-positive patients with normal HER-2 expression six-year survival was significantly longer in patients who received six courses of adjuvant CMFP than in those who received a single course of the same therapy (52% *vs*. 36%). In HER-2 overexpressed patients no benefit was presented (38% *vs*. 29%). This may indicate that HER-2 overexpression is predictive of resistance to CMF. No predictive value of HER-2 was demonstrated in node-negative patients in the same study who were randomized between a single course of perioperative CMFP and observation.

Allred et al. (12) evaluated the relationship between overexpression of HER-2 and the response to adjuvant CMFP therapy in a subgroup of high risk node-negative breast cancer patients. The patients were randomized to be either observed or to receive adjuvant chemotherapy after surgery. While patients with HER-2 negative tumors showed significantly longer DFS (p=0.0003) then their untreated counterparts, patients with HER-2 positive tumors showed a similar DFS with or without treatment, demonstrating no benefit from adjuvant therapy in this subgroup.

In the recently published study by Menard et al. (13), 386 node-positive breast cancer patients were randomly assigned to receive either no further treatment after radical mastectomy or 12 monthly cycles of adjuvant CMF chemotherapy. CMF treatment showed a clinical benefit in the both groups of patients defined according to HER-2 status, proposing no predictive value of HER-2 in terms of resistance to CMF chemotherapy.

Evaluation of the predictive value of HER-2 overexpression in high-risk primary beast cancer patients treated with high-dose chemotherapy with cyclophosphamide, cisplatin and carmustin and autologous stem-cell transplantation in the study by Nieto et al. (14), pointed to HER-2 overexpression as an independent negative predictor of survival in these patients.

HER-2 STATUS AND RESPONSE TO TAXANES

So far, there are little data concerning the role of HER-2 in predicting response to the taxanes.

However, in the study by Baselga et al. (15), archived paraffin-embedded tumor tissue from 122 patients who were treated with single agent paclitaxel or docetaxel was analyzed. Significantly more patients with HER-2 positive tumors than patients with HER-2 negative tumors responded to treatment (64% *vs*. 35%, p=0.02). After adjusting for prognostic factors, it was concluded that the odds for HER-2 positive patients responding clinically were three times higher than of HER-2 negative patients.

The purpose of the study conducted by Sjöstrom et al. (16) was to assess whether HER-2 expression is associated with clinical sensitivity to docetaxel (T) or sequential metotrexate and 5FU (MF). There was no association between treatment outcome and HER-2 overexpression, indicating that HER-2 expression could not predict response to either MF or T.

METHODOLOGICAL LIMITATIONS OF HER-2 PREDICTIVE STUDIES

There are some methodological limitations of current HER-2 predictive studies. None of the studies available were primarily designed to study the role of HER-2 overexpression as a predictive factor. The majority of these studies have been performed as retrospective analyses of prospective clinical trials. Thus, clinical primary endpoints differ from the endpoints used in predictive marker studies, which must allow us to differentiate between the predictive and the prognostic value of HER-2 status. Some statistical issues influence the interpretation of the results of HER-2 predictive studies. Trials performed in metastatic disease are relatively small compared to adjuvant studies, and usually lack statistical power in the subgroup analyses that are required to assess the predictive value of HER-2 status. Some observations come from trials in which only a small number of women had HER-2 measurements and a low prevalence of marker-positivity further reduce the power of the studies. In addition, the accuracy and reproducibility of measurement of HER-2 overexpression, as well as the definition of marker positivity and negativity defined individually by each study, should not be ignored when interpreting the results of HER-2 predictive studies (17).

CONCLUSION

Women whose tumors show HER-2 overexpression are clearly known to be at high risk of recurrence. Results of the studies discussed above are consistent with the conclusions that HER-2 overexpressing tumors are anthracycline responsive (*i.e.*, HER-2 is clearly not a marker of anthracycline resistance), and that patients whose tumors overexpress HER-2 appear to receive the greatest relative benefit from this therapy. At the same time, results of these studies are not conclusive of HER-2 positivity as a marker of absolute sensitivity to anthracyclines (HER-2 positive and negative patients who receive optimal anthracycline doses have similar survival). None of the studies conclusively demonstrates that HER-2 status is able to predict response to anthracycline-based therapy (benefit is seen in both HER-2 positive and HER-2 negative patients). In women whose tumors do not show HER-2 overexpression, regimens such as CMF may be equally effective as anthracycline - containing regimens.

The inconclusive and controversial nature of the studies concerning HER-2 status as a predictor of response to CMF-like therapy and the diametrically opposite results of those studies suggest that there is no definite proof that overexpression of HER-2 is marker of resistance to CMF-like chemotherapy.

Similarly, the predictive value of HER-2 for taxane sensitivity is not yet clear, as some results show that tumors overexpressing HER-2 are not uniformly more sensitive to taxanes.

Finally, in general, HER-2 expression cannot yet be applied clinically as a firm predictive factor to make a choice of drugs either in adjuvant or in metastatic settings of breast cancer patients (6,17-19).

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.

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