



Evidence-based Series #1-17: Section 1

The Role of HER2/*neu* in Systemic and Radiation Therapy for Women with Breast Cancer: A Clinical Practice Guideline

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Questions

In the absence of trastuzumab systemic therapy:

Endocrine therapy

1. Does the efficacy of tamoxifen (compared with no tamoxifen) depend on HER2/*neu* status?
2. Do the relative efficacies of different tamoxifen durations depend on HER2/*neu* status?
3. Do the relative efficacies of aromatase inhibitors (compared with tamoxifen) depend on HER2/*neu* status?
4. Does the efficacy of ovarian ablation (compared with no ovarian ablation) depend on HER2/*neu* status?

Chemotherapy

5. Does the efficacy of anthracycline-based regimens (compared with non-anthracycline-based regimens) depend on HER2/*neu* status?
6. Do the relative efficacies of different anthracycline-based regimens depend on HER2/*neu* status?
7. Does the efficacy of taxane-containing regimens (compared with non-taxane-containing regimens) depend on HER2/*neu* status?
8. Do the relative efficacies of different taxane-containing regimens depend on HER2/*neu* status?

Chemoendocrine Therapy

9. Does the effect of tamoxifen and chemotherapy (compared with tamoxifen alone) depend on HER2/*neu* status?

Radiation Therapy

10. Does the efficacy of radiation therapy (compared with no radiation therapy) depend on HER2/*neu* status?

Target Population

Women with breast cancer.

Recommendations and Key Evidence

Endocrine Therapy - Tamoxifen

Although the current evidence does not support a definitive recommendation regarding tamoxifen therapy and HER2/*neu* status, the weight of the evidence, especially the Gruppo Universitario Napoletano (GUN) trial (1,2), suggests that the efficacy of tamoxifen may be greater in HER2/*neu*-negative patients than in HER2/*neu*-positive patients. However, the evidence does not support a recommendation against tamoxifen therapy in HER2/*neu*-positive patients. While it is possible that tamoxifen is more effective in HER2/*neu*-negative patients, there is still sufficient evidence that it is effective in HER2/*neu*-positive patients as well.

Endocrine Therapy - Aromatase Inhibitors

The current evidence does not support a definitive recommendation regarding aromatase inhibitor therapy and HER2/*neu* status.

Endocrine Therapy - Ovarian Ablation

The current evidence does not support a definitive recommendation regarding ovarian ablation and HER2/*neu* status.

Chemotherapy - Anthracyclines

Patients with HER2/*neu*-positive breast cancer should be considered for chemotherapy containing an anthracycline instead of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) or melphalan and 5-fluorouracil (PF) chemotherapy.

- Ten studies (3-18) of CMF or PF versus an anthracycline-containing chemotherapy were identified that also performed a substudy analysis by HER2/*neu* status. Two of these studies (4,10,14,15) reported a significant interaction between HER2/*neu* status and treatment. A meta-analysis of these studies by HER2/*neu* status found a significant benefit in terms of both overall survival (OS) (hazard ratio [HR] 0.74, 95% confidence interval [CI] 0.63 to 0.87) and disease-free survival (DFS) (HR 0.73, 95% CI 0.63 to 0.85) for the use of anthracycline-based chemotherapy compared to CMF or PF in patients with HER2/*neu*-positive breast cancer, but found no evidence of a benefit in HER2/*neu*-negative patients (HR 1.04 for overall survival, 1.00 for disease-free survival). The interaction between treatment and HER2/*neu* status was found to be significant in the meta-analysis (difference in log OS HRs -0.32 [95% CI -0.51 to -0.12], difference in log DFS HRs -0.29 [95% CI -0.47 to -0.10]).

Qualifying Statements

- Patients with HER2/*neu*-positive breast cancer may derive more benefit from a more intense anthracycline regimen, in terms of dose (i.e., 100 mg/m² epirubicin versus 50 or 60 mg/m² epirubicin) or schedule (i.e., 60 mg/m² epirubicin every 14 days compared to every 21 days), over a less intense one. Four of the identified studies (5,11,19-23) comparing more intense anthracycline-based regimens to less intense ones were identified that also performed a substudy analysis of HER2/*neu* status. Three of these studies (19,21-23) found a significant overall survival benefit for more intense anthracycline regimens versus less intense. A

meta-analysis of these studies by HER2/*neu* status found a significant benefit in terms of DFS (HR 0.53, 95% CI 0.37 to 0.77) for patients with HER2/*neu*-positive breast cancer receiving more intense anthracycline-based chemotherapy. This meta-analysis found no benefit in HER2/*neu*-negative patients (HR 1.09). However, this analysis was found to be sensitive as to which of three different possible sets of hazard ratios were selected in one study (5,11). In that study, the analysis of time-to-progression was conducted using three different methods of HER2/*neu* testing, and the significance of the meta-analysis of the differences in log hazard ratio between the HER2/*neu* subgroups was significant or not significant depending on the choice of testing. Therefore, a firm recommendation was not possible, as absence of interaction could not be definitively rejected.

- The Breast Cancer DSG has produced two separate guidelines on trastuzumab systemic therapy, PG #1-15 (metastatic) and EBS #1-24 (adjuvant), described under “Related Guidelines” below. These guidelines provide important information regarding the use of trastuzumab and anthracyclines sequentially or in combination with regards to concerns about cardiac toxicity. Physicians are encouraged to review the recommendation and qualifying statements in light of the information provided in those guidelines if combination or sequential trastuzumab/anthracycline therapy is being considered. Physicians are discouraged from using trastuzumab concurrently with anthracyclines.

Chemotherapy - Taxanes

The current evidence does not support a definitive recommendation regarding taxane chemotherapy and HER2/*neu* status.

Chemoendocrine Therapy

The current evidence does not support a definitive recommendation regarding chemoendocrine therapy and HER2/*neu* status.

Radiation Therapy

The current evidence does not support a definitive recommendation regarding radiation therapy and HER2/*neu* status.

Related Guidelines

- PG #1-15: *The Role of Trastuzumab (Herceptin®) in the Treatment of Women with HER2/neu-overexpressing Metastatic Breast Cancer.*
- EBS #1-24: *The Role of Trastuzumab in Adjuvant and Neoadjuvant Therapy in Women with HER2/neu-overexpressing Breast Cancer.*

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