The adjuvant treatment of breast cancer human epidermal growth factor receptor (HER2) positive in Albania

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Abstract

Aim: Our aim was to identify and compare the use of Trastuzumab in adjuvant therapy in breast cancer patients who are human epidermal growth factor receptor (HER2) positive in various combinations of chemotherapy regimens.
Methods: The data were retrieved from the medical records of the Chemotherapy Unit at "Mother Teresa" University Hospital Center in Tirana for two consecutive years 2009-2010 including 90 women diagnosed with breast cancer HER2-positive and treated with adjuvant chemotherapy (Trastuzumab). Demographic data, tumor characteristics and disease outcomes for all patients included in this study were also collected.
Results: Chemotherapy was completed in 98% of the patients, while trastuzumab was used in 28 patients, or 31% of them. After 52 months of median follow-up, there were five disease events in the Trastuzumab group (17.8%) and 40 events in the non-Trastuzumab group (64.5%). The hazard ratio (HR) was 0.22 (95%CI: 0.05-0.86; P=0.01).
Conclusion: Our study provides useful evidence on clinical benefits related to the combination of chemotherapy regimens with Taxane and Trastuzumab which indicated an improvement of the disease recurrence compared to regimens without Trastuzumab in this sample of cancer patients in Albania.

Keywords: adjuvant chemotherapy, breast cancer, combination chemotherapy regimens.

Introduction

Breast cancer is a molecularly diverse disease with several defined molecular subgroups. Clinically, however, three therapeutic groups are used: those classified as hormone receptor positive (estrogen receptor and progesterone receptor with normal HER2 expression), those classified as HER2-positive as defined by HER2 amplification, with variable expression of hormonal receptors, or those classified as triple negative by low or absent hormonal receptor and HER2 (1).

More than 1.5 million breast cancer cases are reported each year worldwide and more than 50% are hormone receptor positive, 20%-25% of the cases are HER2-positive and 15% are triple negative (1).

New classes of molecularly targeted therapy can affect the natural history of some groups of breast cancer such as HER2-positive disease both in adjuvant and metastatic disease. Approximately 15%-20% of invasive breast carcinomas have amplification of the human epidermal growth factor receptor 2 gene (HER2-neu) and over-express the HER2 protein (1,2). Before the development of the anti-HER2-targeted therapies, women with early HER2-positive breast cancer faced a worse prognosis in terms of both disease-free (DFS) and overall survival (OS) (1). Three large randomized trials produced convincing evidence that the anti-HER2 monoclonal antibody trastuzumab, administered with adjuvant chemotherapy for 12 months, increases DFS and OS of women with HER2-positive operable breast cancer (2-5). In two of the studies, the NCCTG N9831 and the NSABP B-31, a remarkable increase in 10-year OS from 75% to 84% was recently reported (6). Similarly, significant clinical benefit with adjuvant trastuzumab after chemotherapy was confirmed in a previous report of the HERA trial (2).

The aim of this study was to identify and compare the use of Trastuzumab in adjuvant therapy in breast cancer patients in Albania who are human epidermal growth factor receptor (HER2) positive in various combinations of chemotherapy regimens.

Methods

The data were collected from the cancer registry at the Chemotherapy Unit of the University Hospital Center "Mother Teresa" in Tirana for two consecutive years 2009-2010 including 90 women diagnosed with HER2-positive breast cancer and treated with adjuvant chemotherapy Trastuzumab. Notably, 99% of the patients received adjuvant treatment with chemotherapy and some but not all with Trastuzumab concurrent or sequential with chemotherapy. Women aged 18-75 years old with histologically confirmed invasive early breast cancer with HER2 over-expression were eligible. The HER2-positive status was determined by local pathology laboratories using immunohistochemistry testing. Patients were required to have undergone either lumpectomy or modified radical mastectomy with tumor-free surgical margins plus axillary node dissection, and the tumor had to be invasive carcinoma. Adequate hematologic, hepatic, renal parameters and cardiac function were mandatory. Cardiac function was assessed by an echo-cardiogram procedure, or the left-ventricular ejection fraction (LVEF). All women received epirubicin (75 mg/m^2 by i.v. infusion over 5-15 min), cyclophosphamide (700 mg/m^2 by i.v. infusion over 30-60 min), and 5-fluorouracil (700 mg/m^2 by i.v. infusion over 5-15 min) every two weeks for four cycles followed by docetaxel 75 mg/m^2 by i.v. infusion over 1 h every two weeks for four cycles. Trastuzumab was administered intravenously over 30-90 min every three weeks (loading dose 6 mg/kg; 4 mg/kg thereafter), starting concurrently with docetaxel. Thereafter, trastuzumab 6 mg/kg was administered every three weeks until the completion of 12 months therapy. Radiation therapy was decided by the treating physician and followed the current standards of the "Mother Teresa" University Hospital Center in Tirana.

Patients' follow-up consisted of medical history and physical examination, with laboratory and imaging

studies as indicated, every three months for the first two years, every six months for the next three years and yearly thereafter. Cardiac monitoring was carried out by history, clinical examination, and LVEF assessments every three months and, at the end of treatment, with trastuzumab. Thereafter, cardiac function was assessed only if clinically indicated (e.g. dyspnea, peripheral edema, chest pain, palpitations and the like). Cardiac toxicities were assessed with several indicators including symptoms, a decrease of LVEF under 50% (independent from the baseline value) or an absolute drop of LVEF of more than 15% from baseline.

The primary end point of the study was to compare the 4-year DFS rates between the treatment groups. The DFS was defined as the time from randomization to the date of breast cancer recurrence (either locoregional or distant), contralateral breast cancer diagnosis, non-breast second primary cancer, or death from any cause, whichever occurred first. Patients alive without any predefined event were censored at the time of the last assessment. Secondary end points were to compare the OS (defined as the time from the date of randomization to death from any cause) and toxicity.

Stratification parameters for the random assignment were the number of infiltrated axillary lymph nodes (0 versus 1-3 versus 4-10 versus >10) and hormone receptor status [estrogen (ER) and/or progesterone receptor (PR) positive versus both negative]. All patients who received at least one cycle of treatment were included in the analysis. The DFS and OS rates were calculated using the Kaplan-Meier method. The comparison of treatment arms was assessed using the log-rank test. The independent effect of treatment and other prognostic factors on DFS and OS was analyzed by Cox's proportional hazards model. Quantitative factors were compared by Pearson's $\chi 2$ contingency table analysis or Fisher's test whenever appropriate. P-values ≤ 0.05 were considered statistically significant for all comparisons. The statistical analysis was done in SPSS, version 17.0.

Results

About 32% of the patients received Trastuzumab in addition to chemotherapy in a total of 97 patients (100%) patients. After a median follow-up of 48 months, 5 (17.1%) patients had disease recurrence in the Trastuzumab group and 40 patients (64.5%) in the non-Trastuzumab group (P=0.0001). During this period of time, Trastuzumab was not available for all patients hospitalized at the "Mother Teresa" Hospital in Tirana. The patients treated with Trastuzumab had few events 5 (17.1 %) compared with treatment regimens without Trastuzumab where the number of events was 40 (or, 64.4%). The group treated with CAF consisted of 36 patients and 27 of them had disease recurrence (75.0%). We studied the localization of relapse in this group. The rate of visceral relapse was higher in the HER2-positive group with 32 (64.2%) patients, compared with other localizations of relapse Osseo and loco-regional.

Table 1. Characteristics of HER2-positive patients according to the number of lymph nodes, size of tumor, grade and local treatment (N= 90)

Mastectomy	85 (94.4)
Breast conserving	5 (5.5)
Radiotherapy	23 (25.5)
N0	27 (30.0)
N1-3	18 (20.0)
N 3-10	23 (25.5)
N >10	22 (24.4)
G I	0 (0.0)
G II	42 (46.6)
G III	48 (53.3)
T 1 < 2cm	10 (11.1)
T 2 2-5 cm	71 (78.8)
T3 > 5 cm	9 (10.0)

Table 2. Treatment regimen used in the group of patients HER+/HR

Regimen used	Recurrence	Chi-square	Hazard ratio	95%CI	P-value
AC/T H (4+4) +H N=28	5 (17.8.)*		1		
AC/T (4+4) N=26	13 (50.0)	6.152	0.22	0.05 to 0.86	0.01
CAF (6) N=36	27 (75.0)	22.4	0.07	0.02 to 0.28	0.0001
Total: 90 cases (100%)	45 (50%)				

*Reference group is the regimen AC/T H

Most of the patients undergoing surgical treatment had mastectomy which, under these circumstances, is a commonplace procedure at the University Hospital "Mother Teresa" in Tirana. These cases involved high grade and node-positive tumors in an advanced stage. There were more disease events in the non-Trastuzumab group and they mostly occurred during the first and second year after the diagnosis.

Table 3. The localization of relapse according to regimen used

Recurrence	Loco regional N (%)	Visceral N (%)	Osseo N (%)	Brain N (%)	Total N (%)
AC/T H (4+4) +H N=28	3 (50.0)	3 (9.3)	0 (0.0)	1 (33.3)	7 (100.0)
AC/T (4+4) N=26	2 (30.3)	12 (37.5)	1 (25.0.)	2 (66.7)	17 (100.0)
CAF (6) N=36	1 (16.6)	17 (53.1)	3 (75.0)	0 (0.0)	21 (100.0)
Total	6 (13.3)	32 (71.1)	4 (8.8)	3 (6.6)	45 (100.0)

There was evidence of a high rate of visceral metastases in this group (around 71%) and most of them occurred in the non-Trastuzumab Group. There were some recurrent cases (6.6%) involving the brain.

Discussion

Our findings do not point to an optimal duration of treatment with adjuvant trastuzumab. Hence, this issue remains unclear for our clinical practice. Some observations support trastuzumab administration for a long period. Conversely, in early breast cancer, two small studies have suggested that when trastuzumab is administered concomitantly with chemotherapy for nine weeks to six months, the reduction in the risk of relapse is similar to a longer treatment (7,8). The HERA trial compared 1-year versus 2-year trastuzumab added sequentially to adjuvant chemotherapy and found no additional benefit for the 2-year regimen (4). After a median follow-up of 52 months, DFS events occurred in five patients in the Trastuzumab group (17.4%) and 40 (64.5%) patients in the non-Trastuzumab group. Two-year DFS was 93.8% in the Trastuzumab group and 70% in the non-Trastuzumab group. Fewer patients in the Trastuzumab group had distant recurrences (6.4% versus 8.3%, HR=1.33, 95%CI: 1.04-1.71). Among patients with ER-negative tumors who received only chemotherapy and DFS was significantly shorter in patients of the CAF group compared with those of the Taxane group (HR=1.57, 95%CI: 1.08-2.28). Therefore, in this group of 'pure' HER2-positive tumors, most of the adjuvant effects might occur early during therapy, possibly during the concomitant administration of chemotherapy and trastuzumab (9,10). On the contrary, in the PHARE trial, patients with ER-negative tumors who received trastuzumab sequential to chemotherapy experienced more benefits from the prolonged trastuzumab administration. In our study, the benefit of longer trastuzumab administration almost reached statistical significance (HR=2.20, 95%CI: 0.91-5.31) for patients with ER-negative tumors.

The number of patients enrolled in our study was relatively small and the non-inferiority margin set by the statistical hypothesis was relatively large. Moreover, the study was hampered by a slow accrual and eventually took four years to be completed instead of the planned three years and would have been benefited by an independent review committee which unfortunately was not involved. The two study arms were well-balanced for all the stratification parameters; however, although age was not a stratifying factor, older patients were actually randomized.

Nonetheless, our results indicate that women with small, node-negative tumors have a favorable long-term outcome and if adjuvant therapy is prescribed, then six months of trastuzumab might be a reasonable option. Moreover, in a PHARE trial's date the treatment effect was assessed according to tumors' characteristics and four prognostic groups were defined (very-low, low, intermediate and high) (2).

In conclusion, our results support the current standard of care of 12 months adjuvant trastuzumab for women with early HER2-positive breast cancer. Whether a shorter course of trastuzumab is enough for specific subgroups (e.g. ER-negative tumors, small tumors) needs to be addressed in future clinical studies.

Conflicts of interest: None declared.

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