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OBJECTIVES

The effect of trastuzumab or chemotherapy on cognitive function is not fully understood, especially in elderly patients with breast cancer. The RESPECT trial compared 1-year trastuzumab monotherapy with trastuzumab plus standard chemotherapy as adjuvant therapy in elderly patients with HER2-positive breast cancer. The primary objective was to verify the noninferiority of 1-year trastuzumab monotherapy compared to trastuzumab plus chemotherapy in terms of disease-free survival, and the planned analysis showed that the difference in restricted mean survival times between the two groups at 3 years was 0.45 months (reported by Sawaki at ASCO2018). The goal of this report was to assess the impact of each treatment on longitudinal cognitive function.

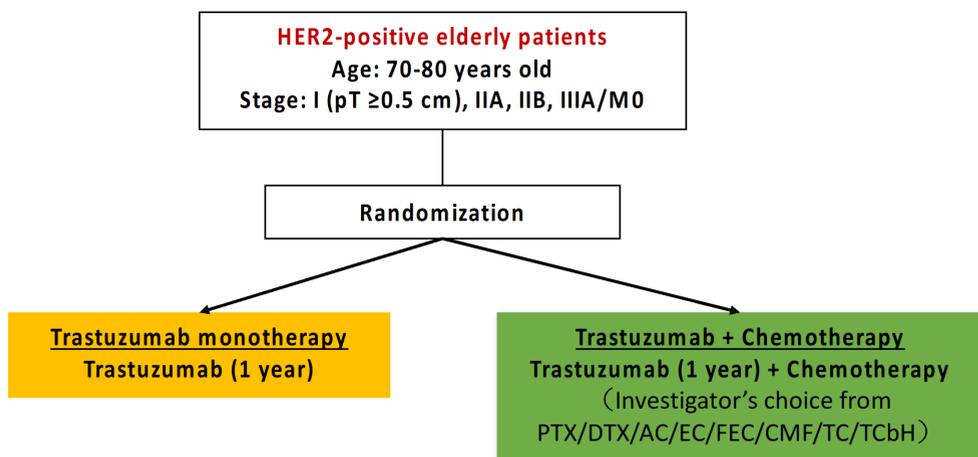


Figure 1. Trial design.

METHODS

Study design

The study was performed at 99 institutions in Japan. Elderly women (70 to 80 years old) with HER2-positive, stage I-IIIa invasive breast cancer treated by surgery with a clear resection margin were randomly assigned to receive 1-year trastuzumab (group H) or 1-year trastuzumab plus standard chemotherapy (group H+CT), stratified by age, hormone-receptor status, pathological lymph node metastasis, and institution (Figure 1). The primary endpoint was disease-free survival (DFS). Secondary endpoints were overall survival, recurrence-free survival, adverse events, PROs/HRQoL, comprehensive geriatric assessment, cognitive function, and cost-effectiveness.

Cognitive function sub-study

Fifteen institutions participated in the cognitive sub-study. Cognitive function was assessed using the Mini-Mental State Examination (MMSE) at baseline (start of protocol treatment) and at 1 and 3 years after treatment.

MMSE: The MMSE is a brief screening test for cognitive deficits that covers a number of domains in orientation, registration, attention and calculation, recall, language, and copying. The MMSE score ranges from 0 to 30, with higher scores indicating better cognitive function. A score ≤ 27 points indicates suspected mild dementia, and a score ≤ 23 points indicates suspected dementia.

Analysis

The primary outcome was the change in MMSE score from baseline. A linear mixed-effects model was used for comparisons of changes in MMSE score between groups, controlling for time and baseline score. Secondary outcomes were the rates of suspected mild dementia (MMSE ≤ 27) and dementia (MMSE ≤ 23) at each time point. This study is registered with ClinicalTrials.gov (NCT01104935).

Table 1. Clinical characteristics of subjects

| Item | Group H (n=29) | Group H+CT (n=26) |
|---------------------------------|----------------|-------------------|
| Age (mean, SD) | 73.6 2.6 | 72.4 2.4 |
| Performance Status | | |
| 0 | 27 93.1% | 24 92.3% |
| 1 | 2 6.9% | 2 7.7% |
| Pathological tumor size | | |
| T1 | 11 37.9% | 14 53.8% |
| T2 | 16 55.2% | 12 46.2% |
| T3 | 2 6.9% | 0 0.0% |
| Lymph node metastasis | | |
| Negative | 24 82.8% | 21 80.8% |
| Positive | 5 17.2% | 5 19.2% |
| Stage | | |
| I | 9 31.0% | 13 50.0% |
| IIA | 17 58.6% | 11 42.3% |
| IIB | 3 10.3% | 2 7.7% |
| Surgery | | |
| Mastectomy | 22 75.9% | 14 53.8% |
| Breast-conserving surgery | 7 24.1% | 12 46.2% |
| Hormone receptor status | | |
| ER-positive and/or PgR-positive | 16 55.2% | 8 30.8% |
| ER- and PgR-negative | 13 44.8% | 18 69.2% |
| Major comorbidity # | | |
| Absent | 12 41.4% | 8 30.8% |
| Present | 17 58.6% | 18 69.2% |
| Chemotherapy regimen | | |
| Taxane | | 15 57.7% |
| Anthracycline | | 7 26.9% |
| CMF | | 4 15.4% |

Major comorbidity, including hypertension, diabetes, osteoporosis, and hyperlipidemia

Characteristics of the patients

Between October 2009 and October 2014, 275 patients were enrolled in the RESPECT trial, and 57 patients were enrolled in the cognitive function sub-study, with 2 patients subsequently excluded. The 55-patient sub-study comprised 29 patients assigned to trastuzumab monotherapy (group H) and 26 assigned to trastuzumab plus chemotherapy (group H+CT). Response rates to the MMSE survey at baseline and at 1 and 3 years were 89.7, 86.2 and 85.7% in group H and 92.3, 65.4, and 87.5% in group H+CT. The characteristics of the 55 patients are shown in Table 1.

Table 2. Analysis of factors that affect the change in MMSE score from baseline using a linear mixed-effects model

| Factor | | |
|-----------------------|-------|--------|
| Group | | |
| Time | | |
| eline score | 63.38 | <.0001 |
| Baseline score × Time | | |

RESULTS

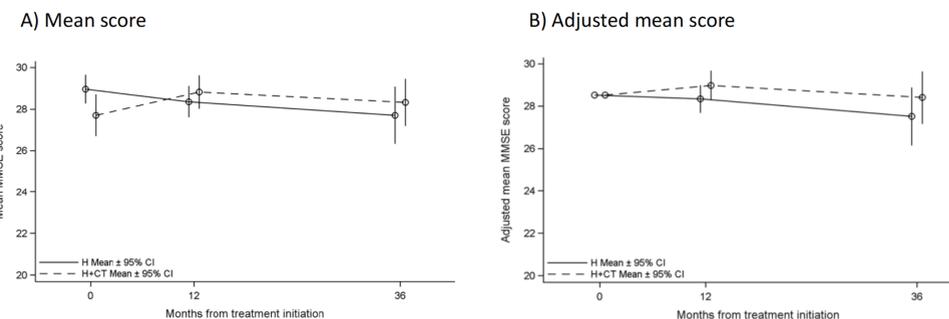


Figure 2. MMSE scores (95% CI) at baseline and at 1 and 3 years. A) Mean score, B) Adjusted mean score

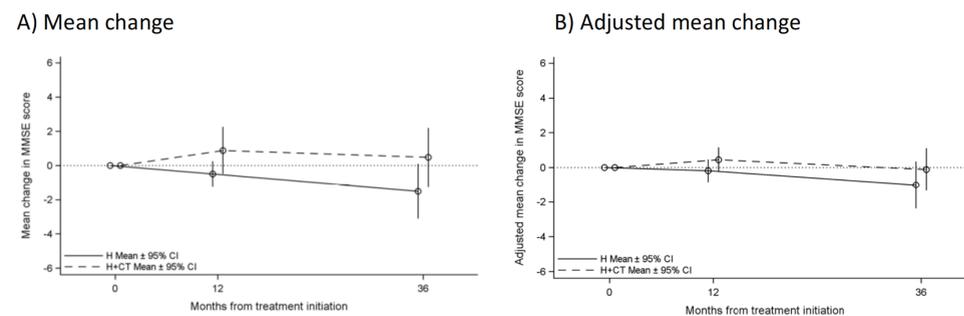


Figure 3. Changes in MMSE scores (95% CI) from baseline at 1 and 3 years. A) Mean change, B) Adjusted mean change

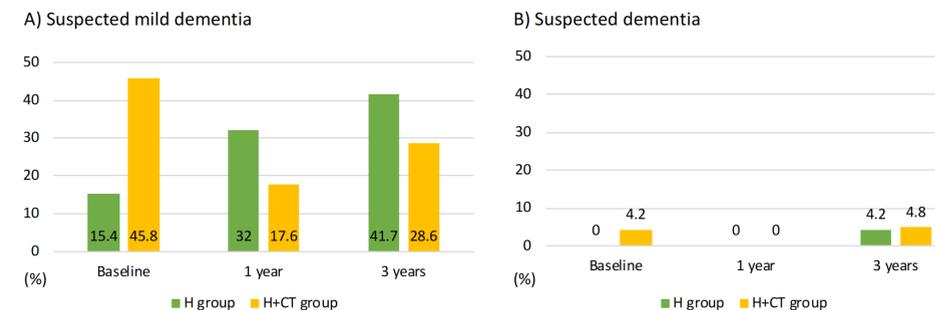


Figure 4. Rates of A) suspected mild dementia (MMSE ≤ 27), and B) suspected dementia (MMSE ≤ 23)

Changes in MMSE scores

The mean MMSE scores at baseline and at 1 and 3 years were 29.0, 28.4 and 27.7 in group H and 27.7, 28.8 and 28.3 in group H+CT (Figure 2). The mean changes of MMSE from the baseline score at 1 and 3 years were -0.5 and -1.5 in group H, and 0.9 and 0.5 in group H+CT (Figure 3). Primary analysis revealed that the change in MMSE score did not differ significantly between the two groups (difference: -0.6 at 1 year and -0.9 at 3 years; $p=0.136$). The baseline score was the only factor that had a significant effect on the change in MMSE score ($p<0.001$) (Table 2).

Patients with suspected mild dementia and dementia

The rates of suspected mild dementia (MMSE ≤ 27) at baseline and at 1 and 3 years were 15.4, 32.0, and 41.7% in group H, and 45.8, 17.6, and 28.6% in group H+CT. The rates of suspected dementia (MMSE ≤ 23) at baseline and at 1 and 3 years were 0%, 0%, and 4.2% in group H, and 4.2%, 0%, and 4.8% in group H+CT, with no significant difference between the treatment groups at each time point.

CONCLUSIONS

This study has a small sample size, but the results suggest that postoperative chemotherapy for elderly patients with breast cancer has little effect on onset of dementia in a follow-up period of 3 years. Further long-term observation is needed to validate this conclusion.

REFERENCES

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