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ORIGINAL ARTICLE

Endocrine therapy alone vs chemotherapy plus endocrine therapies for the treatment of elderly patients with endocrine-responsive and node positive breast cancer: A retrospective analysis of a multicenter study (Anatolian Society of Medical Oncology)

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Summary

Purpose: The extra benefit of adding chemotherapy to effective endocrine therapy (ET) has not been clearly or consistently identified in patients older than 70 years with estrogen receptor (ER) positive and node positive breast cancer. The aim of this study was to evaluate the efficacy of adjuvant ET vs chemotherapy plus endocrine therapies (Chemo/ET) in such patients.

Methods: In this retrospective multicenter study 191 patients ≥ 70 years with operated hormone receptor positive breast cancer, who were administered adjuvant ET or Chemo/ET were assessed.

Results: The median patient follow-up time was 29.0 months (range 1-252). Therefore disease free survival (DFS) and overall survival (OS) analysis was limited, due to the rather short median follow-up, and only 30-month cumulative percentages are reported herein. The 30-month DFS rates were 50.0% in the ET arm and 49.0% in the Chemo/ET arm (p=0.79). The 30-month OS rates were 86% in the ET arm and 96.0% in the Chemo/ET arm (p=0.08). Cox proportional hazard model showed that only surgery was independent prognostic factor for survival (p=0.047), while tumor size showed a strong trend for statistical significance (p=0.051).

Conclusion: The addition of chemotherapy to endocrine therapy in older patients has no significant impact on DFS and OS.

Key words: adjuvant treatment, breast cancer, chemotherapy, elderly patients, hormonal therapy

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Introduction

Breast cancer is the most common cancer and the second leading cause of cancer-related deaths in females [1]. Due to the fact that aging is the principal risk factor for breast cancer, almost half of all breast cancer cases occur in women ≥65 years of age and more than 30% occur in women >70 years of age. Furthermore breast cancer-related mortality increases with age [2]. Despite this pattern of incidence, elderly patients over 70 years of age are generally excluded from randomized clinical trials of breast cancer treatments [3].

The most common presentation of breast cancer in postmenopausal elderly women is an ER positive (ER+) and/or progesterone receptor positive (PR+) tumor and positive hormone receptors are predictive factors of response to hormonal treatments. Endocrine therapies were the gold standard compared with systemic adjuvant chemotherapy in such patients [4-6].

The SEER data demonstrated survival benefit for adjuvant chemotherapy in patients over 70 years with ER negative and node positive breast cancer, whereas differences in ER positive patients were not significant [7]. Nonetheless, the extra benefit of adding chemotherapy to effective ET has not been clearly or consistently identified in patients older than 70 years [8-10]. The few randomized trials that compared chemotherapy plus tamoxifen vs tamoxifen alone did not indicate a significant survival benefit in older women with endocrine-responsive breast cancer [11-15]. A recent meta-analysis found that the addition of chemotherapy to tamoxifen in older women is solely marginally beneficial [16]. There is no consensus regarding such treatment in patients older than 70 years with endocrine-responsive and node positive breast cancer.

We performed a multicenter retrospective analysis of the treatment outcomes of ET vs Chemo/ET in women >70 years of age with endocrine-responsive and node positive breast cancer.

Methods

Inclusion / exclusion criteria

Between January 1990 and April 2012, 191 patients with operated breast cancer recruited from 15 institutions were enrolled onto this retrospective study.

All of the patients met the following inclusion criteria: 1) Age 70 years or older; 2) Histologically confirmed invasive breast cancer; 3) No previous chemotherapy or radiotherapy; 4) Definitive surgical therapy (radical mastectomy or lumpectomy plus axillary dissection); 5) ER+ and/or PR+; 6) Axillary lymph node involvement (at least 5 axillary lymph nodes resected).

Patients treated with neoadjuvant chemotherapy were not included. Patients who had a previous or concurrent second malignancy were excluded.

Factors analysed

Eleven potential prognostic variables were chosen on the basis of previously published clinical trials. The variables were divided into two categories: gender (male or female), Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0-1 vs 2-3), age (>70-80 vs ≥ 81 years), surgery (lumpectomy vs mastectomy), presence of diabetes mellitus (DM) at diagnosis (present vs absent), presence of hypertension (HT) at diagnosis (present vs absent), presence of coronary heart disease (CHD) at diagnosis (present vs absent), number of positive lymph nodes (1-3 vs ≥4), pathologic tumor size (<50 vs ≥50mm), treatment (ET vs Chemo/ET), and type of endocrine treatment (tamoxifen vs aromatase inhibitor).

Treatment

Patients were divided into 2 groups: the ET group was administered tamoxifen or an aromatase inhibitor, whereas the Chemo/ET group received endocrine therapy plus different chemotherapy regimes: AC (doxorubicin + cyclophosphamide); EC (epirubicin + cyclophosphamide), followed by docetaxel q3w; AC followed by weekly paclitaxel; CAF (cyclophosphamide, doxorubicin 5-fluorouracil), followed by taxanes (T); CEF (cyclophosphamide, epirubicin, 5-fluorouracil), TC (docetaxel, cyclophosphamide). In HER2 positive patients trastuzumab was added to the adjuvant chemotherapy regimes.

Statistics

All of the analyses were performed using the SPSS statistical software program package (SPSS version 11.0 for Windows). The differences of the clinical charac-

teristics in both treatment arms were analyzed by the Fisher's exact test. DFS was calculated from the date of operation to the first evidence of recurrence or second primary breast cancer. OS was calculated from the date of operation to the date of death. OS and DFS were calculated with the log-rank test. The Kaplan–Meier method was used to draw survival curves. The Cox proportional hazards regression model was used to statistically determine significant variables related to survival. Differences were assumed to be significant when p value was less than 0.05.

Results

The patient baseline characteristics are listed in Table 1. There were 61 patients in the ET arm (M: 1, F: 60), and 130 in the Chemo/ET arm (M: 7, F: 123). Significantly more patients > 80 years received ET (34.4 vs 12.3%; p=0.001). PS of patients in the Chemo/ET arm was better compared with the ET arm (81.5 vs 87.7%, p=0.003). Patients with >4 positive nodes were more common in the Chemo/ET arm than in the ET arm (43.1 vs 31.1%, p = 0.07). No statistically significant difference was noticed in gender, pathologic tumor size, surgery, type of endocrine treatment, HT and DM between the two groups.

DFS and OS

The median follow-up time was 29.0 months (range 1-252). Therefore, DFS and OS analysis was limited due to the rather short median follow-up and only and 30-month cumulative percentages are reported herein. The 30-month DFS rate was 50.0% in the ET arm and 49.0% in the Chemo/ET arm (p=0.79; Figure 1). The 30-month OS rate was 86% in the ET arm and 96.0% in the Chemo/ET arm (p=0.087; Figure 2).

Prognostic factors analysis

The results of univariate analysis of OS are summarized in Table 2. Among the 11 variables assessed, 3 were identified to have prognostic significance: positive nodes (p=0.04), tumor size (p=0.03) and type of operation (p=0.03).

Multivariate analysis of OS included the 3 significant factors of univariate analysis and the results are shown in Table 3. Cox proportional hazard model showed that only type of surgery was independent prognostic factor for survival (p=0.047), while tumor size showed a strong trend for statistical significance (p=0.051).

The results of univariate analysis of DFS demonstrated that only sex was independent prognostic factor (p=0.001).

Discussion

Aging causes physiologic changes in organ function and drug pharmacokinetics, which can result in reduced therapeutic benefit of chemotherapy [17]. Therefore, in older individuals breast cancer is commonly undertreated. Furthermore, elderly patients over 70 years of age are generally excluded from randomized clinical trials of breast cancer treatments. For this reason, breast cancer in elderly patients is a progressively widespread problem faced by the oncologist.

Several studies demonstrated very different breast cancer outcomes based on patient age; younger patients typically have more aggressive tumors, and older patients more commonly have less aggressive disease.

Elderly patients with early-stage breast cancer receive adjuvant chemotherapy less frequently than younger patients in clinical practice. Results of extra benefit of adding chemotherapy to endocrine-responsive and node positive breast cancer patients older than 70 years are limited and conflicting [11-15]. A recent meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) found that chemotherapy plus tamoxifen in elderly patients is merely marginally beneficial, in contrast to major survival advantages in premenopausal patients [16].

In our retrospective multicenter study, the 30-month DFS rates were similar in both arms (49 vs 50%, p=0.79), while the 30-month OS rates were more favorable in the Chemo/ET arm than the ET alone arm, but the trend did not reach statistical significance (96 vs 86%, p=0.087). The survival rates in the present study were lower than those found in the literature. This result can be explained by the high rate of patients with comorbid diseases such as DM, HT and CHD, the retrospective nature of our study and the short follow-up.

Very different prognostic factors have been identified in several studies with regard to survival in patients with breast cancer; however, only very few studies are

Table 1. Patient characteristics and treatment administered

Characteristics	*Endocrine treatment*		*Chemoendocrine treatment*		*p-value*
	N	*%*	*N*	*%*	
Patients enrolled	61	31.9	130	68.1	
Sex					
Male	1	1.6	7	5.4	>0.05
Female	60	98.4	123	94.6	
Median age, years (range)	76	(70-88)	73.5	(70-88)	
Age (years)					
70-80	40	65.6	114	87.7	0.001
≥81	21	34.4	16	12.3	
ECOG PS					
0-1	35	57.4	106	81.5	0.003
2-3	11	18.0	8	6.2	
Unknown	15	24.6	16	12.3	
Surgery					
Lumpectomy	7	11.5	14	10.8	>0.05
Mastectomy	54	88.5	116	89.2	
Pathologic tumor size (mm)					
<50	47	77.0	107	82.3	>0.05
≥50	10	16.4	22	17.0	
Unknown	4	6.6	1	0.7	
No. of positive nodes					
1-3	42	68.9	74	56.9	0.07
>4	19	31.1	56	43.1	
HT					
Yes	20	32.8	37	28.5	
No	39	63.9	90	69.2	>0.05
Unknown	2	3.3	3	2.3	
DM					
Yes	25	41.0	49	37.7	
No	34	55.7	78	60.0	>0.05
Unknown	2	3.3	3	2.3	
CHD					
Yes	26	42.6	51	39.2	>0.05
No	33	54.1	76	58.5	
Unknown	2	3.3	3	2.3	
Endocrine treatment					
Tamoxifen	11	18.0	40	30.8	0.07
Aromatase inhibitor	50	82.0	90	69.2	

HT: hypertension, DM: diabetes mellitus, CHD: coronary heart disease

dealing with patients older than 70 years with ER positive and node positive disease [15]. Fargeot et al. [15] reported that surgery and the number of positive lymph nodes were independent prognostic factors of OS survival. In the present study, surgery was the only independent prognostic factor for OS (p=0.047), while neither the number of positive lymph nodes p=0.068), nor tumor size impacted significantly OS.

The present study has some limitations. First, it was retrospective in nature; second, the median time of fol-

Table 2. Univariate analysis of overall survival by categorical variable

Variables	*Log-rank*	*DF*	*p-value*
Sex (male vs female)	0.65	1	0.42
Age (70-80 vs ≥ 81 years)	2.30	1	0.12
Performance status (0-1 vs 2-3)	0.64	1	0.42
Surgery (lumpectomy vs mastectomy)	4.63	1	0.03
DM (present vs absent)	0.01	1	0.90
HT (present vs absent)	0.06	1	0.79
CHD (present vs absent)	0.24	1	0.62
Positive nodes (1-3 vs ≥ 4)	3.99	1	0.04
Tumor size (<50 vs ≥ 51mm)	4.54	1	0.03
ET vs Chemo/ET	1.32	1	0.25
Endocrine treatment (Tamoxifen vs aromatase inhib.)	0.12	1	0.72

For abbreviations see footnote of Table 1

Table 3. Multivariate analysis of overall survival

Prognostic factors	*OR*	*95% CI*	*p-value*
Positive nodes (1-3 vs ≥4)	2.40	0.93-6.15	0.068
Tumor size (<50 vs ≥50 mm)	2.90	0.99-8.47	0.051
Surgery (lumpectomy vs mastectomy)	3.77	1.01-14.02	0.047

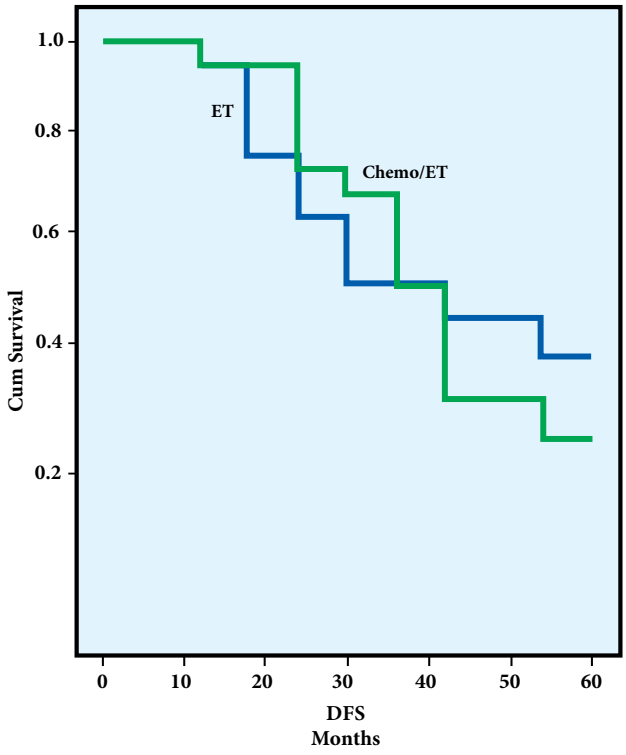

Figure 1. Disease free survival of the endocrine treatment and chemoendocrine treatment groups (p=0.79). ET: endocrine therapy, Chemo/ET: chemoendocrine therapy.

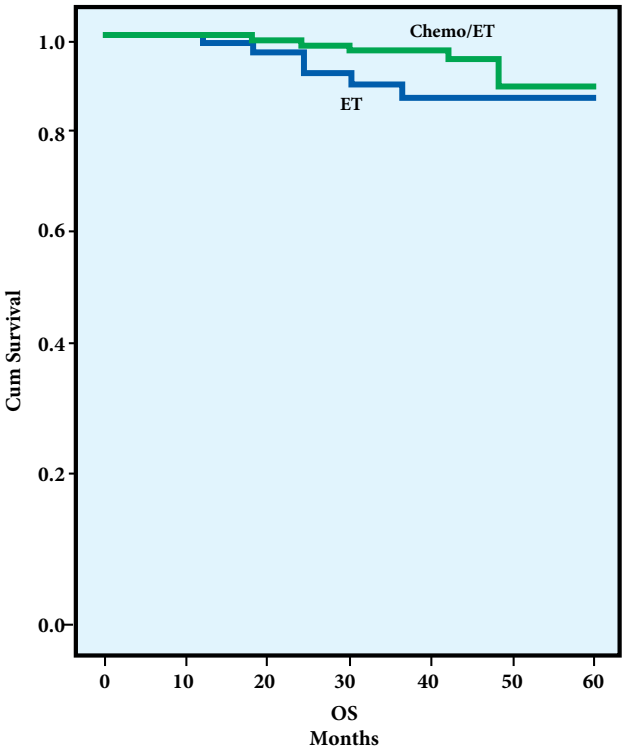

Figure 2. Overall survival of the endocrine treatment and chemoendocrine treatment groups (p=0.08). ET: endocrine therapy, Chemo/ET: chemoendocrine therapy.

low-up was short; third, molecular characteristics of the tumor were not evaluated; and fourth, the number of the patients included was rather small.

In conclusion, the addition of chemotherapy to endocrine therapy in older patients showed no significant positive impact on DFS and OS. For this reason, prospective and larger clinical trials are needed to define the efficacy of the addition of chemotherapy to endocrine therapy for the treatment of patients older than 70 years with ER positive and node positive breast cancer.

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