J Cancer Res Clin Oncol (2016) 142:1847–1853
DOI 10.1007/s00432-016-2194-4

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Adjuvant chemotherapy in elderly patients with primary breast cancer: are women ≥65 undertreated?

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Received: 8 May 2016 / Accepted: 18 June 2016 / Published online: 27 June 2016

Abstract
Purpose To establish whether women over 65 years of age with newly diagnosed with breast cancer (BC) receive adjuvant chemotherapy less frequently than younger postmenopausal women and whether comorbidity influences this potential undertreatment.
Materials and methods In a single-site, retrospective, comparative study, postmenopausal early stage BC patients treated between 01/2001 and 12/2005 at a major German university hospital were analyzed in two age Groups A and B (≥65 vs. <65 years) for initiation and completion of guideline-recommended adjuvant chemotherapy. Risk stratification was based on the 2005 St. Gallen Consensus Conference criteria. Comorbidity was parametrized using the Charlson Comorbidity Index (CCI).
Results Analysis included 634 patients, 380 in Group A and 254 in Group B. Mean age (range) was 73 (65–94) and 61 (55–64) years, respectively. The proportion of patients from Group A given ≥3 cycles of chemotherapy was significantly decreased as compared to Group B. 52 % of patients with CCI <3 but only 20 % with CCI ≥3 were recommended to undergo chemotherapy ($p < 0.001$). Median follow-up [95 % confidence interval (CI)] was 85 (82–88) months. DFS was significantly shorter in patients aged ≥65 years as compared to younger postmenopausal patients (HR, 0.598; 95 % CI, 0.358–0.963; $p = 0.048$).
Conclusions Despite being high-risk patients, older women with early stage BC were often not given guideline-recommended chemotherapy. Higher recurrence rates compared with younger postmenopausal women suggest that older patients are undertreated. Treatment needs to be adapted to general health and tumor biology rather than age. More trials in elderly BC patients are needed.

Keywords Breast cancer · Treatment response · Postmenopausal women · Elderly · Age · Survival

Abbreviations

BC	Breast cancer
CI	Confidence interval
DFS	Disease-free survival
ER	Estrogen receptor
G	Grade
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
OS	Overall survival
pN	Pathologically confirmed nodal status
PR	Progesterone receptor
pT	Pathologically determined tumor size

Introduction

One in eight women develops breast cancer (BC) in the course of her lifetime, with advanced age being one of the major risk factors (Siegel et al. 2015). Half of all women newly diagnosed with BC every year are over 65 years of

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age (Marshall et al. 2010; National Cancer Institute (NCI) 2014). This risk presents a challenge to society as a whole, especially in view of an aging population.

Modern systemic adjuvant treatment has resulted in a continuous increase in life expectance for patients with BC. Over the last decade, numerous new drugs and combinations of drugs have become clinically established based on large prospective multicenter studies. However, the high proportion of older BC patients has been underrepresented in clinical studies (Lewis et al. 2003; Van Ewijk et al. 2015). As a result of a lack of evidence regarding optimal treatment, this patient group often does not receive guideline-based treatment (Schonberg et al. 2010; Yardley 2015).

With increasing age, patients also potentially develop more comorbidities (Extermann et al. 1998). This limits the choice of potential treatment options and negatively affects treatment outcome (Yancik et al. 2001; Bouchardy et al. 2007). The Charlson Comorbidity Index (CCI) represents a standardized and validated tool that enables systematic ascertainment of comorbidities and their effect on mortality. It comprises 22 comorbidities that are assigned severity-based scores. The total score correlates negatively with survival (Charlson et al. 1987).

In this study, we compared the frequency of adjuvant chemotherapy in older patients (>65 years) with younger postmenopausal patients. Against the background of the existing comorbidities, we analyzed whether or not recommended chemotherapy had been initiated and completed as recommended. We also investigated the differences between younger and older postmenopausal patients with respect to disease-free survival (DFS) as well as the effect of classical breast cancer risk factors on prognosis.

Methods

Study design and ethics

The study was a single-site, retrospective, comparative analysis of patient data extracted from the medical records of BC patients treated at Tuebingen University Women's Hospital, Tuebingen, Germany. Ethical approval was obtained in advance from the Ethics Committee of the Medical Faculty of the University of Tuebingen (approval no. 243/2011A).

Patients

Included in the analysis were patients with early stage, primary invasive BC treated at our hospital between January, 2001 and December 2005. Elderly patients aged ≥65 years (Group A) were compared to a younger group of postmenopausal patients aged 55 to <65 years. Patients who were premenopausal, had additional cancers, were DCIS-only, or had metastases, recurrences, or bilateral BC were not included into the analysis.

Data collection

Patient data, tumor characteristics, details of the treatment administered, and survival data were gleaned from the tumor registry of the Tuebingen Comprehensive Cancer Center (CCC) and the patients' medical records and transferred to a database created with Microsoft Access 2010 (Microsoft Corporation, Redmond, WA, USA).

Risk stratification

To reflect the reality of treatment during the study period, patients were assigned to one of the three risk categories (low, intermediate, and high risk) based on the 2005 St. Gallen Consensus Conference (Goldhirsch et al. 2005), as summarized in Table 1.

Charlson Comorbidity Index (CCI)

As shown in Table 2, the CCI divides comorbidities into four categories based on severity, assigning them scores of 1, 2, 3, and 6. CCI total scores were prospectively recorded for patients >65 and, therefore, available for all patients of Group A.

Statistical methods

Statistical analysis utilized PASW Statistics 21 (SPSS Inc., Chicago, IL, USA). Continuous variables were analyzed using mean and standard deviation (SD). Categorical variables were reported as frequency distributions and compared by the Chi squared test. Survival was analyzed in terms of time from primary diagnosis to either disease recurrence (local or distant recurrence), i.e., disease-free survival (DFS), or the patient's death from any cause, i.e., overall

Table 1 Risk categories according to the 2005 St. Gallen Consensus Conference (Goldhirsch et al. 2005)

Risk	Nodal involvement	Tumor size	Grading	HER2 status
Low	pN0	pT1	G1	Negative
Intermediate	pN0	pT1	G2–3	Negative
	pN0	pT2–4	G1–3	Negative
	pN0	pT1–4	G1–3	Positive
	pN1	pT1–4	G1–3	Negative
High	pN1	pT1–4	G1–3	Positive
	pN2	pT1–4	G1–3	

Table 2 Charlson Comorbidity Index (CCI) (Charlson et al. 1987)

Score	Comorbidity
1	Myocardial infarct, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic bronchitis and chronic obstructive pulmonary disease (COPD), connective tissue disease, ulcers, mild liver disease, and diabetes
2	Hemiplegia, kidney disease, diabetes with end organ damage, any tumor, leukemia, and lymphoma
3	Moderate or severe liver disease
6	Tumor metastasis, Acquired Immune Deficiency Syndrome (AIDS)

survival (OS). If neither event occurred, the data were censured at the date of last follow-up. The influence of risk group assignment and treatment received was assessed by univariate analysis based on the hazard ratio (HR) and 95 % confidence interval (CI). Kaplan–Meier curves were constructed and compared by log-rank test. The two-sided significance level was set at $p < 0.05$.

Results

Patient characteristics

In total, 634 patients were included in the analysis, of whom 380 were ≥65 years old and hence assigned to Group A, and 254 were younger than 65 years. Mean age (SD, range) was 73 (6.31, 65–94) years in Group A and 61 (2.27, 55–64) years in Group B.

As shown in Table 3, Group A patients predominantly had invasive ductal tumors (71 %), ≤2 cm in size (51 %),

Table 3 Patients' clinical characteristics and assignment to risk categories

	Group A (≥65 years)	Group B (<65 years)	Total	*p*
Patients, *N*	380	254	634	
Mean age, years (SD)	73 (6.31)	61 (2.27)	68 (55–94)	
Tumor histology, *N* (%)[a]				0.139
Ductal invasive carcinoma	268 (71)	189 (76)	457 (73)	
Lobular invasive carcinoma	81 (21)	49 (20)	130 (21)	
Other	31 (8)	11 (4)	42 (7)	
Tumor size, *N* (%)				<0.001
T1	191 (51)	167 (66)	358 (57)	
T2–4	182 (49)	87 (34)	269 (43)	
Nodal involvement, *N* (%)				0.931
pN−	247 (67)	168 (66)	415 (67)	
pN+	123 (33)	86 (34)	209 (43)	
Grading, *N* (%)				0.029
G1	32 (9)	12 (5)	44 (7)	
G2	309 (83)	206 (81)	515 (82)	
G3	32 (9)	35 (14)	67 (11)	
ER status, *N* (%)				0.004
Negative	43 (11)	50 (20)	93 (15)	
Positive	336 (89)	202 (80)	538 (85)	
PR status, *N* (%)				0.788
Negative	108 (29)	75 (30)	183 (29)	
Positive	270 (71)	177 (70)	447 (71)	
HER2 status, *N* (%)				0.137
Negative	212 (76)	202 (82)	414 (79)	
Positive	67 (24)	46 (19)	113 (21)	
Risk category[a,b], *N* (%)				0.095
Low risk	17 (5)	4 (2)	21 (3)	
Intermediate risk	289 (79)	202 (80)	491 (79)	
High risk	60 (16)	48 (19)	108 (17)	

[a] All percentages are based on the actual number of available data items, not on group size

[b] According to the 2005 St. Gallen Consensus Conference (Goldhirsch et al. 2005)

grade G2 (83 %). Most patients were node negative (67 %) and HER2 negative (76 %). Accordingly, the majority of patients (79 %) were in the intermediate risk category. Hormone receptor status was mostly positive for estrogen receptor (ER; 89 %) and progesterone receptor (PR; 71 %). The comparison group of younger patients, Group B, had a similar proportion of patients (76 %, $p = 0.139$) with invasive ductal carcinoma. However, there were significantly more high grade tumors ($p = 0.029$) and ER-negative carcinomas ($p = 0.004$). In Group B, tumors <2 cm were less frequent than in Group A (66 %, $p < 0.001$). Nodal involvement, HER2 status, and PR status did not differ significantly between Groups A and B. Similarly to Group A, most (80 %) patients in Group B were in the intermediate risk category.

Chemotherapy

Compared with the younger postmenopausal patients in Group B, the older Group A patients in both the intermediate and high risk categories received chemotherapy less frequently (Table 4). Only 18 % of Group A patients compared with 56 % of Group B patients received ≥3 cycles of chemotherapy ($p < 0.001$). This difference was particularly marked in the intermediate risk category (16 vs. 55 %, $p < 0.001$).

As shown in Table 5, 111 patients from Group A received a recommendation to undergo chemotherapy but only 67 patients completed ≥3 cycles, while 6 patients discontinued chemotherapy earlier and 38 patients did not even start treatment.

Recommendation for chemotherapy was significantly associated with the presence of comorbidity in both intermediate and high risk patients, as shown in Table 6. Whereas 52 % of patients aged ≥65 years with a CCI <3 were recommended to undergo chemotherapy, only 20 % of elderly patients with a CCI ≥3 were advised to do so ($p < 0.001$).

Survival analysis

Median follow-up was 85 (95 % CI, 82–88) months. Figure 1 compares DFS in Groups A and B. DFS was significantly shorter in the older patients of Group A (HR, 0.598; 95 % CI, 0.358–0.963; $p = 0.048$).

Table 5 Chemotherapy recommendations for patients ≥65 years

	N (%)
Chemotherapy recommended	111 (100)
≥3 cycles completed	67 (60)
<3 cycles completed	6 (6)
Not started	38 (34)

Table 6 Chemotherapy recommendation for patients ≥65 years, by CCI

	CCI < 3	CCI ≥ 3	*p*
All risk categories[a]	58/112 (52)	53/268 (20)	<0.001
Intermediate risk	47/97 (49)	34/203 (17)	<0.001
High risk	11/11 (100)	19/45 (42)	<0.001

[a] According to the 2005 St. Gallen Consensus Conference (Goldhirsch et al. 2005)

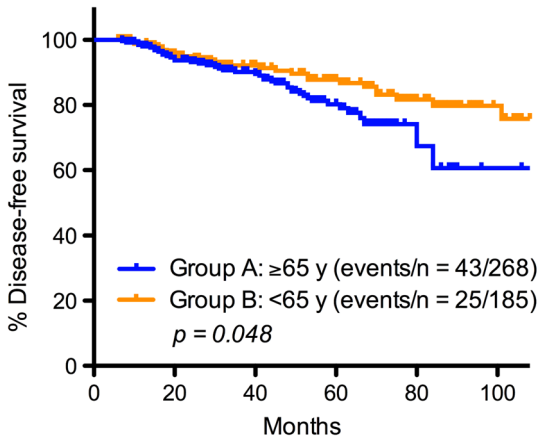

Fig. 1 Disease-free survival in Groups A and B

Figure 2 shows a comparison of DFS (panel A) and OS (panel B) in low/intermediate risk patients as versus high risk patients from Group A. Both DFS (HR, 0.112; 95 % CI, 0.049–0.256; $p < 0.001$) and OS (HR, 0.218; 95 % CI, 0.111–0.426; $p < 0.001$) were found to be significantly decreased in high-risk elderly patients.

Table 4 Patients given at least three cycles of chemotherapy, by age and risk category

	Group A (≥65 years) *N* (%)	Group B (<65 years) *N* (%)	All ages *N* (%)	*p*
All risk categories[a]	67/366 (18)	140/254 (56)	207/634 (34)	<0.001
Low risk	0/17 (0)	0/4 (0)	0/21 (0)	
Intermediate risk	46/289 (16)	110/202 (55)	157/491 (32)	<0.001
High risk	20/60 (33)	30/48 (67)	50/108 (48)	0.001

[a] According to the 2005 St. Gallen Consensus Conference (Goldhirsch et al. 2005)

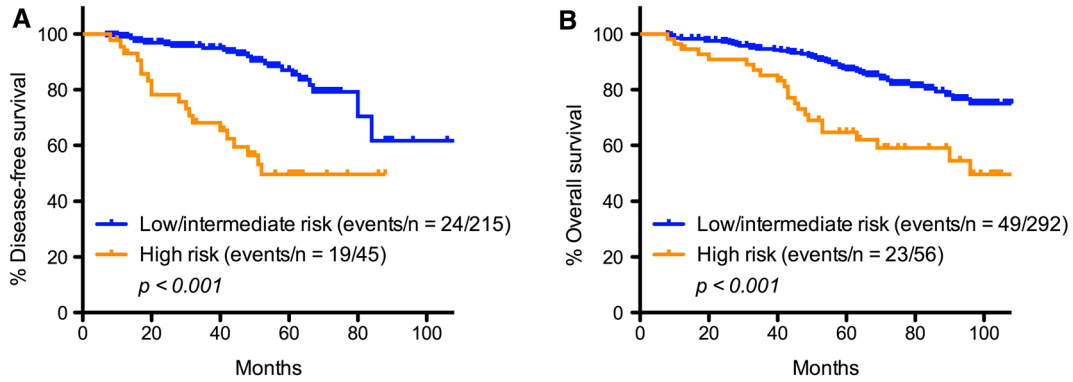

Fig. 2 Disease-free survival (**a**) and overall survival (**b**) in low and intermediate risk patients (combined) compared with high risk patients from Group A

Discussion

The present analysis revealed that among postmenopausal patients with early stage primary BC treated at our hospital during 2001–2005 those aged ≥65 years (Group A) received adjuvant chemotherapy significantly less frequently than younger postmenopausal patients (Group B). At the same time, DFS was significantly shorter in the group of older women.

Several retrospective studies investigating the use of adjuvant chemotherapy in elderly patients have reported different treatment rates in the range from 5 to 32 % (Vlastos et al. 2001; Woodard et al. 2003; Brunello et al. 2005; Hawfield et al. 2006; Peters et al. 2015). However, these studies are not readily comparable due to differences in age distributions and patient characteristics. Nonetheless, in all studies, advanced age was a frequent reason to dispense with adjuvant chemotherapy, independently of comorbidities and prognostic factors.

To reflect the reality of treatment during the study period, this study divided patients into three risk categories—low, intermediate, and high risk—based on the 2005 St. Gallen Consensus Conference (Goldhirsch et al. 2005). There was no significant difference between the Group A and the Group B patients with regard to patient assignment to one of the three risk categories. As in other studies, older patients more frequently had larger tumors, which, however, tended to be less aggressive, i.e., G3 or hormone receptor-negative (Schonberg et al. 2010; Pappo et al. 2007; Diab et al. 2000). These observations indicate that diagnosis of BC is often delayed in elderly patients.

The observation that older patients aged ≥65 years received adjuvant chemotherapy less frequent than younger postmenopausal patients was noted across all risk categories. Similarly, the presence of comorbidities was associated with the absence of adjuvant chemotherapy in all risk categories. However, due to the retrospective nature of our study, we were unable to investigate in detail any additional factors that may have influenced the decision to proceed or not to proceed with chemotherapy.

Comorbidity was not associated with increased discontinuation of chemotherapy in our analysis (data not shown). Similar results were reported by Klepin et al. (2014), who showed that both chemotherapy tolerance and DFS were not negatively affected by comorbidity. However, when interpreting the data published by Klepin et al., it should be noted that patients in their study had an excellent performance status. As regards our own study, those patients who actually started chemotherapy presumably had a better performance status than did those for whom chemotherapy was not a treatment option. In contrast, other retrospective studies found a high CCI to be associated with an increased discontinuation rate, dose reduction, and grade 3–4 toxicity (Garg et al. 2009; Zauderer et al. 2009).

High-risk elderly patients aged ≥65 years (Group A) experienced a significantly worse outcome than did intermediate or low-risk patients. Hence, high-risk patients seem to require more aggressive or more effective treatment. Our finding that DFS was significantly longer in the younger postmenopausal patients (Group B) indirectly suggests that the older patients were potentially undertreated. A multicenter cohort study by Van Ewijk et al. (2015) showed guideline-adherent treatment to be associated with an improved prognosis. In a prospective randomized study, Muss and colleagues (Muss et al. 2009) compared capecitabine with standard polychemotherapy in older patients with early stage BC. They observed that patients treated with capecitabine alone had significantly shorter survival than patients receiving aggressive chemotherapy. In particular, hormone receptor-positive, node-negative women appeared to derive the greatest benefit from chemotherapy. Of note, while quality of life was decreased during treatment with the more aggressive

regimen due to its higher toxicity, quality of life 1 year after treatment was the same in both arms of the study (Kornblith et al. 2011).

Limitations of this study include its retrospective nature and the fact that the data were collected during the 2001–2005 period. While this enabled a longer follow-up, modern and in particular targeted treatments, were not available yet at the time of data collection. A direct analysis of the extent to which chemotherapy might benefit older patients in terms of a better prognosis cannot be performed because other factors that also determine prognosis have a decisive influence on the decision whether or not to recommend chemotherapy. Although appropriate in this situation, a multivariate analysis cannot meaningfully be performed due to the great number of factors to be investigated and the limited number of cases available. We also did not compare survival in Groups A and B because older patients per se have a shorter life expectancy and BC-specific survival data were not available.

Conclusions

Our study showed that older BC patients with early stage disease often do not receive chemotherapy even if they are high-risk patients. The higher recurrence rate compared with younger postmenopausal women suggests that older patients are undertreated. Even though the actual impact of undertreatment on prognosis may be difficult to judge, no patient should be refused guideline-adherent treatment merely on the basis of age. Rather, treatment needs to be adapted to the patient's general state of health and tumor biology.

In the future, predictive tests will be able to better estimate the actual benefit a treatment may provide and a larger number of targeted drugs with fewer adverse effects will come into use. Against this backdrop, there is a need for more clinical trials with a focus on the continually growing population of elderly BC patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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