Metastatic breast cancer — age has a significant effect on survival

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Summary

The data on 217 elderly (aged ⩾ 65 years) and 209 middle-aged postmenopausal patients with metastatic breast cancer treated in the Department of Medical Oncology, University of Pretoria, from 1976 to 1985 were analysed to determine the effect of age on survival. When considered as a group, the elderly have a more favourable prognosis (median survival 20,3 months) than the middle-aged (median survival 15,54 months) ($P = 0,0457$). Multivariate age subset analysis (taking into account all other major prognostic factors) reveal a distinct bimodal pattern. The median survival of patients aged 45 - 54 years is 21,2 months and decreases to 16,2 months for patients aged 55 - 64 years ($P = 0,08$; Cox model). The median survival improves again to 24,6 months for patients aged 64 - 74 years ($P = 0,0001$; Cox model), followed by an apparent but non-significant decrease to 17,1 months in the very old (aged 75 - 84 years) ($P = 0,52$; Cox model). The more favourable prognosis in the elderly dictates effective non-toxic treatment.

Breast cancer is the second most common cause of death in the elderly. The correct initial management of patients with metastatic breast cancer is of prime importance to ensure prolonged, meaningful survival without undue toxicity. The natural history of breast cancer in the elderly is therefore of importance. The effect of age on the prognosis of metastatic breast cancer is controversial. Some reports indicate no effect of age on prognosis,[1] others a worse[2,3] and some a better prognosis with increasing age.[4] Many series have the inherent defect of not simultaneously considering all important co-variates in order to delineate exactly the effect of age as an independent factor. Others do not have enough elderly patients in their series to reach firm conclusions. The present study was undertaken in a large series of elderly patients in which an adequate comparison with middle-aged postmenopausal patients with metastatic breast cancer could be made.

Patients and methods

Data on all evaluable elderly patients (⩾ 65 years) with metastatic breast cancer seen in the Department of Medical Oncology, University of Pretoria, from January 1976 to December 1985 were analysed. All evaluable middle-aged patients (< 65 years of age but post-menopausal) with metasta-

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tic breast cancer seen in the same period were included in the analysis as a comparative group.

Factors taken into consideration included: age group, associated disease (other medical disorder resulting in little or severe disability),[5] hormone receptor status, performance status, dominant metastatic site, number of metastatic sites, and treatment. The patient characteristics and treatment are shown in Table I. There were 217 elderly and 209 middle-aged patients. The median age of the elderly was 72 years and the median age of the middle-aged was 57 years. More elderly patients (13%) had significant disability due to associated disease compared with the middle-aged (1%). There was no significant difference in the incidence of associated disease within the elderly subgroups. In both groups the oestrogen receptor (ER) status was largely unknown (85% and 83%). Within the elderly group, patients aged 85+ years had a higher rate of ER positivity (33%) than those aged 75 - 84 years (19%) and those aged 65 - 74 years (9%). The performance status (PS) (Eastern Cooperative Oncology Group[6]) distribution was similar in the elderly (50%, PS1) and middle-aged (53%, PS1). The distribution of the dominant metastatic sites were similar — bone metastases in 32% of the elderly and 30% in the middle-aged patients.

The number of metastatic sites were comparable, 50% of the elderly and 49% of the middle-aged had only 1 metastatic site. Fifty-three per cent of the elderly were treated with tamoxifen, while 59% of the middle-aged were treated with cytostatic and hormonal agents (cyclophosphamide, methotrexate, 5-fluorouracil, prednisone, fluoxymesterone and tamoxifen was the most commonly used treatment regimen).

Statistical methods. Descriptive statistics and survival functions were done with the BMDP L-program using the Kaplan-Meyer survival curve.[7] The Mantel-Cox test[8] was used for survival differences (non-cancer deaths were regarded as censored observations). The simultaneous effects of several factors were explored using the Cox proportional hazards model.[9]

Results

There was a significant difference in the median survival of the elderly group (20,3 months) v. that of the middle-aged (16,54 months) (Mantel-Cox $P = 0,0457$). Within the elderly group the median survival of the 65 - 74-year-olds was 24,6 months, that of the 75 - 84-year-olds 17,1 months and that of the 85+ year-olds 39,8 months. Within the middle-aged the median survival of the 45 - 54-year-olds was 21,2 months and that of the 55 - 64-year-olds 16,2 months (Table I).

The effect of the other prognostic factors on survival are also shown in Table I. Significant factors favourably influencing survival are: good PS (elderly and middle-aged $P ⩽ 0,0001$); bone as dominant metastatic site (elderly $P ⩽ 0,0001$, middle-aged $P = 0,0139$); and small tumour burden — few metastatic sites (elderly $P = 0,0056$, middle-aged $P = 0,0089$). There was a significant association between treatment and survival in the elderly patients. Elderly patients treated with hormones only had a significantly better survival (31 months) than elderly patients treated with chemotherapy plus hormones (18,5 months) or chemotherapy only (19,9 months) ($P = 0,0054$). In

TABLE I. PATIENTS, TREATMENT CHARACTERISTICS AND SURVIVAL

	Elderly patients			Middle-aged patients		
	No.	%	Survival (mo.)	No.	%	Survival (mo.)
Age group (yrs)						
45-54	—			61	29	21,2
55-64	—			148	71	16,2
65-74	153	71	24,6	—		
75-84	53	24	17,1	—		
85 +	11	5	39,8	—		
Associated disease						
None	103	47	23,4	138	66	17,5
Present with:						
little disability	86	40	26,2	69	33	17,2
significant disability	28	13	20,2	2	1	10,4
ER status						
Positive	26	12	29,4	21	10	22,3
Negative	6	3	16,3	15	7	10,7
Unknown	185	85	22,7	181	83	17,5
Performance						
PS 0 (no symptoms)	24	11	59,2	43	21	30,4
PS 1 (ambulant)	110	50	23,9	111	53	20,4
PS 2 (in bed 50%)	47	22	20,5	29	14	12,8
PS 3 (in bed 75%)	21	10	6,0	17	8	8,9
PS 4 (bedridden)	15	7	4,1	9	4	1,1
Dominant metastatic site						
Visceral	80	37	14,4	79	38	10,4
Bone	69	32	22,7	63	30	25,3
Soft tissue	68	31	27,2	67	32	21,0
No. of metastatic sites						
1	109	50	25,6	103	49	21,2
2	59	27	25,7	65	31	16,5
3	34	15	16,3	30	15	12,1
4 or more	15	7	2,2	11	5	2,7
Treatment						
Chemotherapy only	43	19	19,9	51	24	12,2
Chemotherapy plus						
hormones	60	28	18,5	124	59	18,8
Hormones only	114	53	31,0	34	17	16,6

the middle-aged there was no significant difference between the various treatment groups.

Associated disease and ER status did not have a significant effect on survival. When exploring the simultaneous effect of all these factors on survival (with the elderly and the middle-aged grouped together) it was shown that good PS was the most important favourable factor influencing survival ($P \leqslant 0,0001$) (Table II). Bone as dominant metastatic site was second in importance ($P = 0,001$) and older age as a favourable prognostic factor entered as the third most important factor ($P = 0,007$). Fewer metastatic sites ($P = 0,037$) came fourth in importance.

The effect of age on survival was further examined in the Cox model (Table III). This allowed simultaneous considera-

TABLE II. IMPORTANCE OF PROGNOSTIC FACTORS FAVOURABLY INFLUENCING SURVIVAL IN A MULTIVARIATE MODEL

	P
Good performance status	0,001
Bone dominant metastases	0,001
Older age group	0,007
Few metastatic sites	0,037

TABLE III. PROGNOSTIC FACTOR-CORRECTED AGE-GROUP COMPARISON

Age group (yrs)	P value for survival
45-54 v. 55-64	0,0870
45-54 v. 65-74	0,3221
45-54 v. 75-84	0,2610
45 v. 85 +	0,4013
55-64 v. 65-74	0,0001
55-64 v. 75-84	0,0030
55-64 v. 85 +	0,0280
65-74 v. 75-84	0,5205
65-74 v. 85 +	0,5558
75-84 v. 85 +	0,9398

tion of all the major prognostic factors, thus giving the 'pure' effect of age. A definite bimodal pattern of survival emerged. Patients aged 45 - 54 years had a median survival of 21,2 months which decreased to 16,2 months for patients aged 55 - 64 years ($P \leqslant 0,08$; Cox model). The median survival improved

again to 24,6 months in patients aged 65 - 74 years ($P \leqslant$ 0,0001; Cox model) followed by an apparent but non-significant decrease to 17,1 months in the very old, aged 75 - 84 years ($P = 0,5205$; Cox model). There were too few patients in the 85+ year-old group for meaningful comparison.

Discussion

This series consists of a large number of patients treated in the Department of Medical Oncology, University of Pretoria. Univariate analysis showed that the elderly as a group had a more favourable prognosis (median survival 20,3 months) than the middle-aged (16,54 months) ($P = 0,0457$). When examining the effect of age on survival, it is necessary to take into account all the other major prognostic factors that may influence survival. In the present series, the other classic factors, such as PS ($P = 0,0001$), bone as the dominant metastatic site (elderly $P = 0,0001$, middle-aged $P = 0,0139$), and a small tumour burden — few metastatic sites (elderly $P = 0,0056$, middle-aged $P = 0,0089$) had similar significance in both the elderly and the middle-aged. These factors were therefore considered together with age in a Cox model. Older age emerged as the third most important favourable prognostic factor ($P = 0,007$) after good PS and bone as the dominant metastatic site. Age subset analysis (with the Cox model) showed a bimodal pattern: the median survival of patients aged 45 - 54 years (21,2 months) decreases nearly significantly to 16,2 months in patients aged 55 - 64 years ($P = 0,08$). The median survival then increases in the elderly subset, 65 - 74 years, to 24,6 months ($P = 0,0001$) and this is followed by a non-significant decrease ($P = 0,52$) to 17,1 months in the age subset 75 - 84 years. This apparent decrease is clearly related to other prognostic factors and does not reflect more aggressive biological behaviour in the elderly.

ER status was not shown to effect survival in this study. This is due to the large proportion of patients with unknown ER status (ER status measurement was rarely performed in the earlier years of the study). In the patients with known ER status, there was an increase in ER positivity with age, which could explain the increase in survival with increasing age.

The recognition of this bimodal pattern explains the conflicting results in published reports on the effects of age in metastatic breast cancer. It is evident that the prognosis varies according to the selection of age interval. Clark et al.[1] found no significant effect of age — which is to be expected as the dividing point was older or younger than 50 years of age. Nash et al.[2] described an increase in survival up to the age of 60 years and a decline afterwards, which may fit in with the bimodal pattern described in this series. No subset analysis was performed in patients > 60 years.

Falkson et al.[4] reported on 1 168 patients with recurrent breast cancer. The study on patients entered on Eastern Cooperative Oncology Group (ECOG) protocols showed that younger patients (in a Cox proportional hazards model of survival) had shorter survival times. The predicted median survival times after the first recurrence were 491 days for patients < 35 years of age, 590 days for patients 36 - 45 years, and 700 days for those > 45 years. In that series there were, however, only 79 patients > 65 years of age. In the univariate analysis the 75 patients aged 66 - 80 years had a median

survival of 22,8 months. This pattern fits well with the present series. The main difference between the two series is that the ECOG patients were selected for study and did not have concomitant other disease (which excluded most elderly patients for entry on study). The present series included all evaluable patients seen at a single institution.

Host and Lund[3] studied an unselected series of 31 594 patients with breast cancer. The only co-variate considered together with age was stage of disease. They found a decline in survival in all stages of breast cancer in the age subset of 50 - 74 years. A similar decline was observed in patients aged 55 - 64 years of the present series, but improvement occurred again in the elderly subset of 65 - 74 years. This subset was not separately analysed by Host and Lund.[3] Host and Lund[3] ascribed the decline in survival after 50 years of age to a possible change in hormonal balance. Since all our patients were postmenopausal, this phenomenon is more likely to be a pure age-related change.

In the present series elderly patients treated with hormones only (mainly tamoxifen) had a significantly better median survival (31 months) than patients treated with chemotherapy only (19,9 months) or chemotherapy plus hormones (18,5 months) ($P = 0,0054$). In the middle-aged there was no significant difference between the various treatment groups. Hormonal treatment is the first line treatment of choice in the elderly with metastatic breast cancer. This is in agreement with a randomized trial by Taylor et al.[10] It can be concluded that as a group the elderly with metastatic breast cancer have a better overall prognosis than postmenopausal women < 65 years of age as a group. A bimodal pattern is evident when age subsets are fully analysed — a better prognosis is seen in the 45 - 54-year-old subset with a decline in prognosis in the 55 - 64-year-old group of patients. An increase in prognosis again occurs in all further elderly subsets when considered with multivariate analysis. These findings reconfirm the age influence on prognosis when all elderly patients with adequate data are included in the analysis. The elderly deserve optimal non-toxic treatment for metastatic breast cancer.

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