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Effect of Age on Overall Survival in Capecitabine-treated Patients With Metastatic Breast Cancer

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Background

- As monotherapy[1] and in combination with a taxane,[2] capecitabine (C) has been shown to improve overall survival (OS) in patients with metastatic breast cancer (mBC).
- Breast cancer occurs across a broad age spectrum and the risk and incidence increase with each decade of life after the age of 40 years.
- This exploratory analysis was conducted to see if an association exists between age and C efficacy as measured by OS and clinical benefit rate among patients with mBC treated with C.

Methods

- We analyzed data from the intermittent dose arms (2510 mg/m^2/d) 2 weeks on/1 week off of 5 phase 2/3 monotherapy or combination therapy with C registration trials involving patients with mBC.[3-7] These trials involved a large number of patients, but did not capture all of the data included in more recent trials.
- The intent-to-treat (ITT) population in this analysis was defined as all randomized patients who took at least 1 dose of study medication.
- Patients were divided into 3 groups by age: 18-49, 50-64, and 65 years or older.
- The Kaplan-Meier method was used to estimate the age-category-specific survival by trial.
- Cox proportional hazard regression analysis was conducted to investigate the effect of age on OS using pooled data from the 5 trials with stratification by trial. Univariate and multivariate models using key baseline characteristics were produced.
- Univariate and multivariate logistic regression was used to investigate the effect of age on clinical benefit and objective response rates.

Results

Baseline Characteristics

- A total of 570 ITT patients were included in the analysis (median age, 55 years [range, 26-83 years]).
  - Of these, 193 (34%) were 18-49 years old; 246 (43%) were 50-64 years old, and 131 (23%) were ≥65 years old.
- A baseline Karnofsky score ≥90 was observed in 68.5%, 57.4%, and 52.0% of patients 18-49, 50-64, and ≥65 years old, respectively.
- There were significant differences among the groups with respect to race, body mass index, number of metastatic sites, time since diagnosis, time from diagnosis to recurrence, and Karnofsky score (Table 1).

Table 1. Baseline Characteristics

	Age Group (y)		
	18-49 (n = 193)	50-64 (n = 246)	≥65 (n = 131)
Body mass index (BMI), kg/m^2			
Median	(n = 191) 24.6	(n = 244) 26.9	(n = 129) 25.9
Range	16-43	15-46	16-42
BMI group, n (%)			
Underweight	7 (3.7)	2 (0.8)	2 (1.6)
Normal weight	95 (49.7)	83 (34.0)	56 (43.4)
Overweight	58 (30.4)	90 (36.9)	44 (34.1)
Obese	31 (16.2)	69 (28.3)	27 (20.9)
Primary breast cancer subtype, n (%)			
Ductal	154 (79.8)	179 (72.8)	99 (75.6)
Lobular	5 (2.6)	20 (8.1)	10 (7.6)
Medullary	1 (0.5)	0	2 (1.5)
Tubular	0	0	0
Mucinous	2 (1.0)	0	0
Comedo	1 (0.5)	2 (0.8)	1 (0.8)
Inflammatory	6 (3.1)	7 (2.8)	2 (1.5)
Mixed ductal/lobular	7 (3.6)	8 (3.3)	4 (3.1)
Other	17 (8.8)	30 (12.2)	13 (9.9)
Predominant site of disease, n (%)			
Bone	5 (2.6)	18 (7.3)	8 (6.1)
Soft tissue	48 (24.9)	55 (22.4)	33 (25.2)
Visceral	140 (72.5)	173 (70.3)	90 (68.7)
Number of metastatic sites			
Mean (SD)	3.3 (1.6)	3.1 (1.8)	3.6 (1.8)
Range	1-9	0-9	1-11
Categorical number of metastatic sites, n (%)			
<3	64 (33.2)	111 (45.1)	40 (30.5)
≥3	129 (66.8)	135 (54.9)	91 (69.5)
Time since diagnosis, d			
Median	891	1160.5	1308
Range	81-5501	11-9225	4-10,398
Categorical time since diagnosis, n (%)			
<24 mo	74 (38.3)	79 (32.1)	37 (28.2)
≥24 mo	119 (61.7)	167 (67.9)	94 (71.8)
Time from diagnosis to recurrence, d	(n = 167)	(n = 206)	(n = 115)
Median	642	800.5	927
Range	64-5168	28-7398	9-9146
Categorical time from diagnosis to recurrence, n (%)			
<1 year	32 (16.6)	38 (15.4)	22 (16.8)
≥1 year	135 (69.9)	168 (68.3)	93 (71)
Missing	26 (13.5)	40 (16.3)	16 (12.2)
Karnofsky score	(n = 184)	(n = 242)	(n = 127)
Mean (SD)	89.6 (9.3)	86.9 (9.8)	85.9 (9.7)
Range	70-100	70-100	70-100
Karnofsky score group, n (%)			
70-79	13 (7.1)	31 (12.8)	18 (14.2)
80-89	45 (24.5)	72 (29.8)	43 (33.9)
90-100	126 (68.5)	139 (57.4)	66 (52.0)

Treatment

- Median treatment duration, number of treatment cycles, and median cumulative dose are summarized in Table 2.

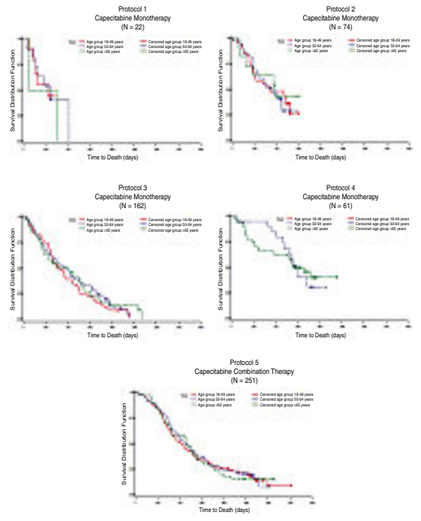
Table 2. Treatment

	Age Group (y)		
	18-49 (n = 193)	50-64 (n = 246)	≥65 (n = 131)
Treatment duration, d			
Median	93	110	80
Range	2-397	2-448	5-371
95% CI	105.9-133.8	110.7-134.0	92.2-126.1
Number of cycles			
Median	4	5	4
Range	1-16	1-16	1-16
95% CI	5.1-6.4	5.3-6.4	4.4-5.9
Cumulative dose, mg/m^2			
Median	128,623	139,077	109,091
Range	142,724-178,254	146,542-175,151	125,078-164,097
95% CI	142,723.6-178,253.9	146,542.2-175,150.5	125,077.6-164,097.3

Efficacy Outcomes

- Univariate and multivariate analyses (data not shown) demonstrated no difference in clinical benefit (Table 3) or objective response (Table 4) for the groups aged either 18-49 or 50-64 years compared with the ≥65-year-old group.
- Unadjusted log-rank tests for each of the 5 trials showed no significant differences in OS among age categories.
- Kaplan-Meier plots of OS by age group for each of the 5 trials showed no significant difference among age categories (Figure).

Figure. Survival Distribution Function by Age Group



- In pooled analysis, univariate Cox regression did not detect significant differences in survival based on age (Table 5).
- Cox model revealed consistent results after further controlling for available baseline characteristics.

Table 3. Logistic Regression Results Modeling Clinical Benefit Rate to Capecitabine Treatment, Univariate Results

	Effect of Age on Clinical Benefit Rate[a] (n = 499)			
Age (y)	Beta	OR[b]	95% CI (OR)	P Value
18-49 vs ≥65	-0.3215	0.725	0.387-1.360	0.3164
50-64 vs ≥65	0.0657	1.068	0.586-1.947	0.8301

[a]Clinical benefit consists of complete response, partial response, and stable disease; n = number of patients in the model.
[b]Odds ratios (OR), confidence intervals (CI), and P values are from a conditional logistic regression model stratified by protocol with a single covariate modeling the probability of clinical benefit to capecitabine. Missing data are excluded.

Table 4. Logistic Regression Results Modeling Objective Response to Capecitabine Treatment, Univariate Results

	Effect of Age on Objective Response[a] (n = 499)			
Age (y)	Beta	OR[b]	95% CI (OR)	P Value
18-49 vs ≥65	0.1799	1.197	0.6979-2.112	0.5346
50-64 vs ≥65	0.1618	1.176	0.692-1.997	0.5496

[a]Objective response consists of complete response and partial response; n = number of patients in the model.
[b]Odds ratios (OR), confidence intervals (CI), and P values are from a conditional logistic regression model stratified by protocol with a single covariate modeling the probability of objective response to capecitabine. Missing data are excluded.

Table 5. Cox Regression Results of Overall Survival, Univariate Results

	Effect of Factors on Overall Survival (n = 570)	
Covariate	HR (CI)	P Value
Age 18-49 y	1.069 (0.811-1.408)	0.6364
Age 50-64 y	0.994 (0.769-1.286)	0.9640
Age ≥65 y	Reference cell	—

CI, confidence interval; HR, hazard ratio.

Study Withdrawal

- A total of 461 patients (81%) withdrew from the study (Table 6).
  - Of these, 347 (61%) withdrew for non-safety reasons, 114 (20%) for safety reasons.
- Insufficient therapeutic response was the most frequent reason for study withdrawal, accounting for 111 (57.5%), 125 (50.8%), and 47 (35.9%) patients in the groups aged 18-49, 50-64, and ≥65 years, respectively.
- An adverse event (AE) was the reason for study withdrawal in 25 (13.0%), 37 (15.0%), and 32 (24.4%) patients in the groups aged 18-49, 50-64, and ≥65 years, respectively.

Table 6. Reason for Study Withdrawal

	Age Group (y)			
	18-49 (n = 193)	50-64 (n = 246)	≥65 (n = 131)	All Ages (n = 570)
Safety, n (%)	32 (17)	45 (18)	37 (28)	114 (20)
Abnormal laboratory test	2 (1.0)	3 (1.2)	1 (0.8)	6 (1)
Adverse event[a]	25 (13.0)	37 (15.0)	32 (24.4)	94 (16)
Death	5 (2.6)	5 (2.0)	4 (3.1)	14 (2)
Non-safety, n (%)	135 (70)	151 (61)	61 (47)	347 (61)
Insufficient therapeutic response	111 (57.5)	125 (50.8)	47 (35.9)	283 (50)
Protocol violation	0	1 (0.4)	0	1 (0.2)
Refused treatment[b]	11 (5.7)	11 (4.5)	9 (6.9)	31 (5)
Failure to return	1 (0.5)	1 (0.4)	1 (0.8)	3 (0.5)
Other	12 (6.2)	13 (5.3)	4 (3.1)	29 (5)
TOTAL	167 (87)	196 (80)	98 (75)	461 (81)

[a]Including intercurrent illness.
[b]Including "did not cooperate," "withdrew consent."

Safety

- An AE occurred in 191 (99%), 242 (98%), and 126 (96%) patients in the 18-49, 50-64, and ≥65-year-old groups, respectively.
- A serious AE occurred in 71 (37%), 85 (35%), and 59 (45%) patients in the 18-49, 50-64, and ≥65-year-old groups, respectively (Table 7).
  - Febrile neutropenia was the most common AE in the group aged 18-49 years, diarrhea in the group aged 50-64 years, and dehydration in the ≥65-year-old group.

Table 7. Summary of Serious Adverse Events With an Incidence ≥5%

	Age Group (y)		
	18-49 (n = 193)	50-64 (n = 246)	≥65 (n = 131)
Diarrhea	8 (4%)	18 (7%)	10 (8%)
Vomiting	7 (4%)	13 (5%)	7 (5%)
Stomatitis	6 (3%)	9 (4%)	8 (6%)
Febrile neutropenia	18 (9%)	16 (7%)	4 (3%)
Dyspnea	9 (5%)	10 (4%)	3 (2%)
Dehydration	2 (1%)	12 (5%)	11 (8%)

Conclusions

- No statistically significant effect of age on OS, clinical benefit, or objective response was observed in patients with mBC treated with C.
- There was a nonstatistically significant trend for a lower median cumulative dose and shorter median treatment duration in patients ≥65 years old compared with each of the other 2 groups.
- In patients ≥65 years old, withdrawal from the study was more commonly due to an AE and less commonly due to insufficient therapeutic response compared with the other 2 groups.
- These results suggest that OS does not differ across predefined age groups of patients with mBC treated with C.

References

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