Identifying Risk Factors For Toxicity in Patients With Hormone Receptor Positive Advanced Breast Cancer Treated With Bevacizumab Plus Letrozole: A CALGB 40503 (Alliance) Correlative Study

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Alliance Cancer in the Elderly Committee Meeting, May 13, 2016

Background

- Bevacizumab has been associated with increased incidence of arterial thromboembolic events
  - Pooled analysis from 5 randomized control trials
  - 1745 patients with various metastatic carcinomas including breast cancer

- Significant risk factors:
  - Older adults age $\geq$ 65 years
  - Prior arterial thromboembolic event

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Scappaticci et al. JNCI 2007

Background

- CALGB 40503 (Alliance): Four month progression free survival benefit with addition of bevacizumab (B) to 1st line letrozole (L) in hormone receptor positive (HR+) advanced breast cancer

- Increased grade ≥3 bevacizumab-related adverse events (AEs) reported with combination therapy:
  - Hypertension (23% vs 2%)
  - Proteinuria (11% vs 0%)

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Dickler et al. ASCO 2015

Background

- CALGB 40503 (Alliance): One treatment-related death (0.6%) due to CNS hemorrhage in the L+B treatment arm

- LEA study: Eight treatment-related deaths (4.2%) in the bevacizumab plus endocrine therapy arm
  - Six deaths were cardiovascular events
  - Six patients were older adults: age ≥ 70 years

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Dickler et al. ASCO 2015
Martin et al. J Clin Oncol 2015

Primary Study Objective

- To identify factors other than chronological age that may predict grade ≥ 3 toxicity in patients receiving L +B
- Key factors include:
  - Functional status:
    - Instrumental activities of daily living (OARS-IADL)
    - Medical Outcomes Study (MOS) Physical Functioning
    - Karnofsky Performance Status (KPS)-MD Rated
    - Timed “Up and Go”
  - Commorbidity: OARS Physical Health Section

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Secondary Study Objective

- To perform an exploratory analysis of whether other factors included in patient pretreatment geriatric assessment (GA) questionnaire (either individually or in combination) can predict risk of grade $\geq$ 3 toxicity in patients receiving L+B

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Hypothesis

- In addition to chronologic age, measures of functional age can be used to identify patients at risk for toxicity while receiving L+B for HR+ advanced breast cancer

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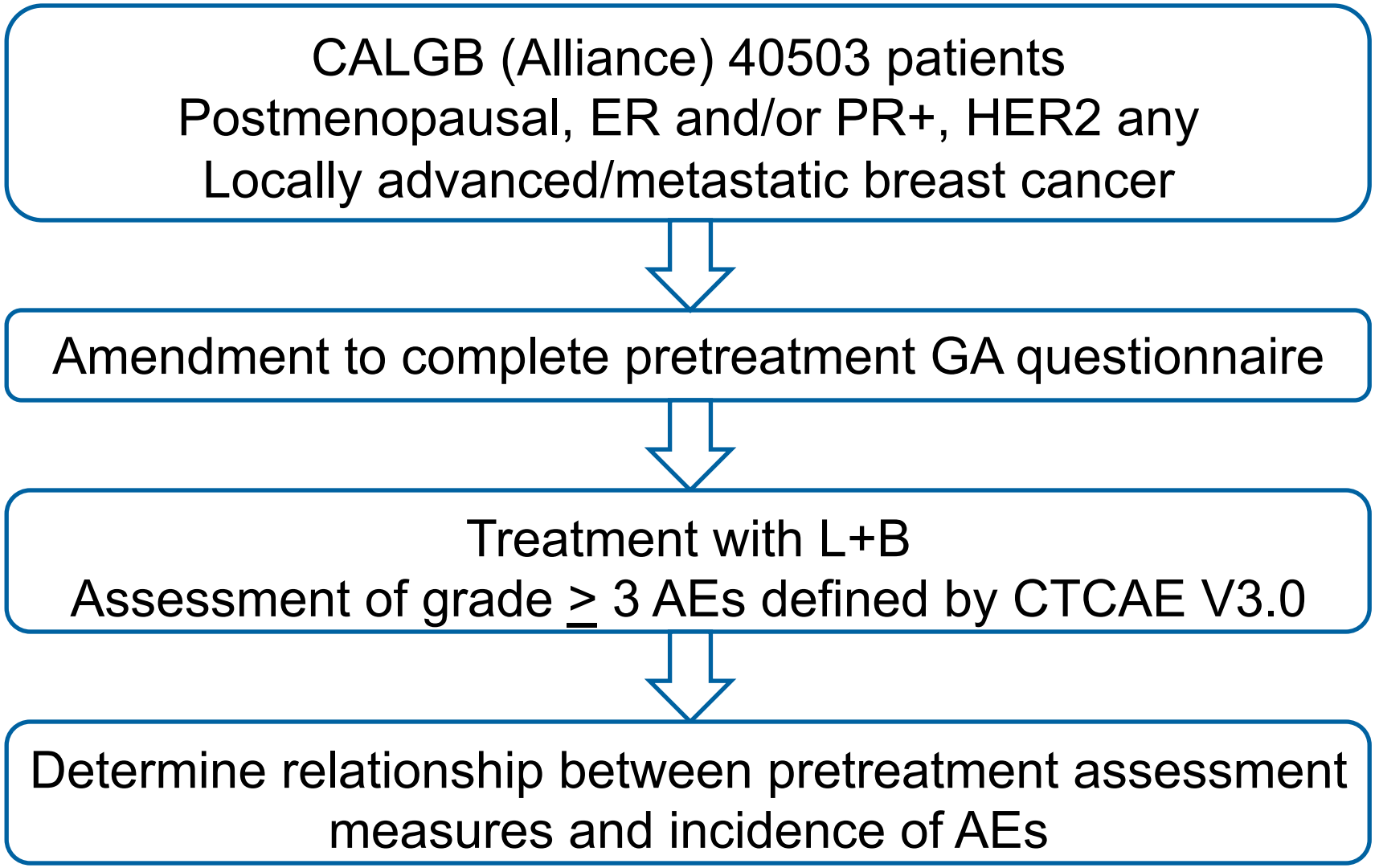
Patients and Methods



GA Questionnaire Domains & Measures

Domain	Measure
Functional Status	Activities of Daily Living (subscale of MOS Physical Health)
	Instrumental Activities of Daily Living (subscale of the OARS)
	Karnofsky Physician-Rated Performance status
	No. of falls in last 6 months
	Timed Up & Go
Cognition	Blessed Orientation-Memory-Concentration Test (BOMC)
Comorbidity	Physical Health Section (subscale of the OARS)
Psychological State	MHI Depression and Anxiety
Social Activity	MOS Social Activity Survey
Social Support	MOS Social Support Survey: Emotional/Information and Tangible Subscales
Nutrition	Body Mass Index
	Percent unintentional weight loss in last 6 months

Statistical Analysis

- Chi square or Fisher's exact tests were used to compare baseline characteristics and incidence of AEs between patients completing baseline GA vs patients with no baseline GA
- Chi square, Fisher's exact test, and univariable logistic regression was used to examine univariable association between the presence of grade $\geq$3 AEs and GA variables. Multivariable logistic regression was performed to explore more than one GA variable at the same time

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Patient Characteristics

	Baseline GA (N=228)	No Baseline GA (N=163)	P-Value
Treatment Arm			0.73
Bevacizumab plus letrozole	112 (49.1%)	83 (50.9%)	
Letrozole alone	116 (50.9%)	80 (49.1%)	
Race			0.31
White	207 (92.0%)	141 (89.2%)	
Other	18 (8.0%)	17 (10.7%)	
Age			0.63
<65	170 (74.6%)	125 (76.7%)	
≥65	58 (25.4%)	38 (23.3%)	
Performance Status			0.015
0	153 (67.1%)	89 (56.7%)	
1	75 (32.9%)	65 (41.4%)	
2	0 (0%)	3 (1.9%)	
Missing/Unknown	0 (0%)	6 (3.7%)	
Receptor Status			
ER+	227 (99.6%)	157 (96.3%)	0.99
PR+	186 (81.7%)	117 (74.5%)	0.053
Her-2+	12 (5.5%)	6 (4.0%)	0.50
Grade ≥ 3 AEs	101 (44.3%)	77 (52.7%)	0.11

Patient Characteristics

Treatment Arm Completing GA	Bevacizumab plus Letrozole (N=112)
Age: Median (range) <65 ≥65	55.5 (24.7-85.3) 87 (77.7%) 25 (22.3%)
KPS 100 90 80 70	 63 (56.2%) 35 (31.2%) 10 (8.9%) 4 (3.6%)
OARS IADL-Completely Independent	76 (67.9%)
Comorbidity-OARS Physical Health Section 0 1 2 or more	 76 (67.9%) 19 (17.0%) 17 (15.2%)
MOS Physical Functioning: Median (range)	90 (5-100)
Timed Up and Go (seconds): Median (range)	10 (2-60)
Falls in past 6 months None One or more	 88 (78.6%) 22 (19.6%)

Patient Characteristics

Treatment Arm Completing GA	Bevacizumab plus Letrozole (N=112)
Hearing Excellent/Good Fair/Poor/Deaf	 97 (86.6%) 14 (12.5%)
Vision Excellent/Good Fair/Poor/Blind	 99 (88.4%) 12 (10.7%)
MHI Depression and Anxiety: Median (range)	81.2 (21.2-100)
MOS Social Activity: Median (range)	50 (25-75)
MOS Social Support: Median (range)	97.9 (22.9-100)
BOMC Cognition Score <11 ≥11	 108 (96.4%) 1 (0.9%)
Baseline BMI <22	17 (15.4%)
Baseline BMI ≥30	46 (41.8%)
Greater than 5% weight loss	0 (0%)

Grade ≥ 3 Adverse Events

Bevacizumab+Letrozole Patients	Total N=112	Percentage (%)
Total		
Grade 3 Event	55	49.1%
Grade 4 Event	5	4.5%
Grade 5 Event	1	0.9%
Hematologic Adverse Events		
Grade 3 Event	3	2.7%
Grade 4 Event	1	0.9%
Grade 5 Event	0	0%
Non-Hematologic Adverse Events		
Grade 3 Event	54	48.2%
Grade 4 Event	4	3.6%
Grade 5 Event	1	0.9%

Frequent and Notable Adverse Events

Type of Adverse Event	Grade 3	Grade 4	Grade 5
Hypertension	27 (24%)	2 (2%)	0 (0%)
Pain	22 (20%)	0 (0%)	0 (0%)
Proteinuria	8 (7%)	0 (0%)	0 (0%)
Nausea	5 (4%)	0 (0%)	0 (0%)
Syncope	3 (3%)	0 (0%)	0 (0%)
Cardiac Ischemia/Infarction	1 (1%)	0 (0%)	0 (0%)
Hemorrhage	1 (1%)	0 (0%)	0 (0%)
Thrombosis	1 (1%)	0 (0%)	0 (0%)
Hypoxia	0 (0%)	0 (0%)	1 (1%)

Additional Grade 4 events included: 1 hypocalcemia, 1 neurologic event, and 1 neutropenia

Risk Factors For Toxicity: Univariable Analysis

Risk Factors	p-value
Age	0.0035
Decreased Vision	0.036
Lower Instrumental Activities of Daily Living Scores (OARS IADL)	0.023
Lower Activities of Daily Living Scores (MOS Physical Functioning)	0.023
Needing help getting to places out of walking distance	0.02
Limitation in climbing flights of stairs	0.016
Limitation climbing one flight of stairs	0.037
Limitation walking more than one mile	0.041

Multivariable analysis: Age $\geq$65 (p=0.014) and decreased vision (p=0.038) remained as significant risk factors for toxicity

Association Between Model Variables

	Age	Vision	IADL: out of walking distance help	Climbing flights of stairs	Medication help	Mile walk
Age	----	0.82	<0.0001	0.018	0.045	0.005
Vision		----	0.028	0.0003	0.60	0.007
IADL: out of walking distance help			----	<0.001	<0.0001	<0.0001
Climbing flights of stairs				----	0.024	<0.0001
Medication help					----	0.067
Mile walk						----

Chi square or exact p-values listed

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Univariable Models

Risk Factors	OR (95% CI)	c-statistic
Age (≥65)	3.93 (1.24-9.31)	0.597
Decreased Vision	4.70 (0.98-22.58)	0.562
IADL: Needing help getting to places out of walking distance	5.28 (1.11-25.06)	0.570
MOS: Limitation in climbing flights of stairs	3.14 (1.41-6.99)	0.635
MOS: Limitation walking more than one mile	2.67 (1.21-5.87)	0.617

Limitations in climbing flights of stairs or walking more than one mile are more strongly associated with AEs compared to age

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Multivariable Models with Age

Risk Factors	c-statistic
Age (≥65)	0.597
Age (≥65) Decreased Vision	0.646
Age (≥65) IADL: Needing help getting to places out of walking distance	0.632
Age (≥65) MOS: Limitation in climbing flights of stairs	0.670
Age (≥65) MOS: Limitation walking more than one mile	0.659

Addition of functional variables to age improve models in predicting AE risk compared to age alone

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Limitations

- Selective group of patients
  - Young (median age 55)
  - Good performance status (All with ECOG 0-1)

- Modest toxicity to L+B treatment regimen
  - Hypertension
  - Proteinuria
  - Treatment related death: 1 vs 8 deaths reported in prior LEA study

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Limitations

- Lack of power to detect additional risk factors of toxicity on multivariable analysis:
  - Modest number of older adults (25 patients ≥65)
  - Many GA variables strongly associated with age and with each other causing difficulty to build multivariable model

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Conclusions

- Potential risk factors of toxicity in patients receiving L+B:
  - Older age
  - Decreased vision
  - Impairment in physical function
- Incorporation of functional age assessment should be used to identify patients at serious AE risk in clinical trials

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