Accrual of Older Breast Cancer Patients to Alliance Systemic Therapy Trials over Time: Protocol A15127

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Accrual of Older Patients to Clinical Trials is Persistent Challenge

Fig 1. Age distribution for patients enrolled onto National Cancer Institute (NCI) adult cooperative group phase II and III treatment trials (all diseases) from 2001 to 2011. Percentage of patients enrolled in each age group is shown for each year, as reported by cooperative groups to the NCI Clinical Data Update System database (NCI Division of Cancer Treatment and Diagnosis) as of May 2012.

Hurria et al JCO 2014; U13 conference recommendations
Study Objectives

• To describe the proportion of patients 65+ and 70+ enrolled to breast cancer systemic therapy clinical trials within the Alliance during 1985-2012

• To compare disease characteristics of older vs. patients enrolling on Alliance studies

• To compare the reasons for protocol therapy cessation for older vs. younger trial participants
Methods (1)

• Reviewed Alliance trial portfolio for adjuvant, neoadjuvant, metastatic trials
• Focused on systemic treatment trials (not supportive care)
## Neo/Adjuvant Trials Included

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Agents given</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adjuvant Trials</strong></td>
<td></td>
</tr>
<tr>
<td>CALGB 40101</td>
<td>AC vs. T (4 vs. 6 cycles)</td>
</tr>
<tr>
<td>CALGB 49907</td>
<td>AC/CMF vs. capecitabine</td>
</tr>
<tr>
<td>N9831</td>
<td>ACT vs. ACTH</td>
</tr>
<tr>
<td>CALGB 9344</td>
<td>AC with 3 different doses of A (60, 75, 90 mg/m2) x 4 cycles +/- T</td>
</tr>
<tr>
<td>CALGB 9741</td>
<td>ACT on q2 vs. q3 week schedule vs. sequential ATC</td>
</tr>
<tr>
<td>NCCTG 89-30-52</td>
<td>Tam +/- fluoxymesterone</td>
</tr>
<tr>
<td>CALGB 8541</td>
<td>CAF dosing</td>
</tr>
<tr>
<td><strong>Neoadjuvant trials</strong></td>
<td></td>
</tr>
<tr>
<td>CALGB 40603</td>
<td>ACT +/- carbo +/- bev</td>
</tr>
<tr>
<td>CALGB 40601</td>
<td>TH vs. THL vs. TL</td>
</tr>
<tr>
<td>ACOSOG Z1041</td>
<td>Preop FEC--&gt;TH vs. TH--&gt;FEC+H</td>
</tr>
<tr>
<td>ACOSOG Z1031</td>
<td>Preop exemestane, letrozole, anastrozole in postmenopausal pts.</td>
</tr>
</tbody>
</table>
## Metastatic Trials Included

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Agents given</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metastatic trials</strong></td>
<td></td>
</tr>
<tr>
<td>CALGB 40503</td>
<td>Let/tam +/- bev</td>
</tr>
<tr>
<td>CALGB 40502</td>
<td>Weekly paclitaxel vs. nab-paclitaxel vs. ixabepilone</td>
</tr>
<tr>
<td>CALGB 40302</td>
<td>Fulvestrant +/- lapatinib for Postmenopausal patients</td>
</tr>
<tr>
<td>CALGB 9342</td>
<td>Paclitaxel dosing</td>
</tr>
<tr>
<td>CALGB 9840</td>
<td>Paclitaxel schedules (q1 vs. q3 week) + trastuzumab</td>
</tr>
</tbody>
</table>
Methods (2)

• Primary endpoint
  – Proportion of older patients enrolled onto studies over time, using the date of protocol registration for each patient
    • Overall and by trial type (adjuvant/neoadjuvant/metastatic)
    • By age 65+ and 70+

• Secondary endpoints
  – Disease characteristics and ECOG PS by age
  – Reasons for cessation of treatment by age
Statistical Analysis

- Modeled age as a function of time using logistic regression for age ≥65 (vs. <65) and age ≥70 (vs. <70)
  - Separate models for adjuvant, neoadjuvant, and metastatic trials
  - Sensitivity analysis after excluding CALGB 49907, NCCTG 89-30-52, ACOSOG Z1031 because these trials enrolled patients age ≥65 at rates of 100%, 70%, and 52%

- Compared ER/PR/HER2 status, mean tumor size, number of nodes involved on adjuvant studies
  - Chi-squared tests for comparisons of receptor status
  - Paired t-tests for comparisons of tumor size and nodes

- Compared ECOG PS by age using chi-square tests (when info available)

- Compared reasons for therapy cessation by age (chi-squared tests) for all studies combined and for each trial type separately
Dates of Accrual for Each Study

- CALGB 40603
- CALGB 40601
- CALGB 40502
- CALGB 40503
- ACOSOG Z1041
- ACOSOG Z1041
- CALGB 40302
- CALGB 40101
- CALGB 49907
- N9831
- CALGB 9840
- CALGB 9741
- CALGB 9342
- CALGB 9344
- NCCN- 89-30-
- CALGB 8541

Years:
- 1985
- 1988
- 1990
- 1993
- 1996
- 1999
- 2002
- 2005
- 2008
- 2011
Proportion (%) of those Age 65+ (blue bars) and 70+ (red bars) Enrolled to Clinical Trials by Trial Type
Unadjusted % of older patients enrolled over time for 65+ and 70+ (Overall, across all trials)
Unadjusted % of older patients enrolled over time for 65+ and 70+ by Trial Type

Proportion of Patients Aged 65+ Enrolled to Trials Over Time By Trial Type

Proportion of Patients Aged 70+ Enrolled to Trials Over Time By Trial Type
Accrual After Exclusion of 49907, NCCTG 89-30-52, and Z1031
Results from Models: OR for Enrollment

OR for enrolling for age ≥65 vs. age <65:

- Significant increase by year in adjuvant trials  
  - OR=1.04 (95% CI=1.04-1.05; p<.0001)
- Significant decrease by year in neoadjuvant and metastatic trials  
  - OR=0.62, 95% CI=0.58-0.67; p < 0.0001 (neoadjuvant)  
  - OR=0.98, 95% CI=0.97-1.00; p=.03 (metastatic)
- Similar trends for age ≥70, but were statistically significant for adjuvant and neoadjuvant trials only  
  - OR=1.05, 95% CI=1.04-1.07 (adjuvant)  
  - OR=0.57, 95% CI=0.52-0.62 (neoadjuvant)
- After exclusion of 49907, NCCTG 89-30-52, and ACOSOG Z1031, results were similar for adjuvant and metastatic trials, but not significant for neoadjuvant trials
Secondary Endpoints (Summary)

• In general, mean number of nodes was statistically higher across all adjuvant studies for older vs. younger patients

• For ECOG PS, those age ≥65 and ≥70 had higher proportions of participants with ECOG PS 1 (vs. 0) on CALGB 40101, 40302, 40503, and 40603 compared with younger women
## Reasons for Therapy Cessation by Age

<table>
<thead>
<tr>
<th>Reason for going off study</th>
<th>Total N (%) (all ages) (N=13763)</th>
<th>Age &lt;65 (n, %) (N=11336)</th>
<th>Age &gt;=65 (n, %) (N=2427)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies combined</td>
<td>(N=13763)</td>
<td>(N=11336)</td>
<td>(N=2427)</td>
<td>&lt;0.00011</td>
</tr>
<tr>
<td>Adverse event</td>
<td>911 (6.6)</td>
<td>720 (6.4)</td>
<td>191 (7.9)</td>
<td></td>
</tr>
<tr>
<td>Completed per protocol</td>
<td>8481 (61.6)</td>
<td>7267 (64.1)</td>
<td>1214 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>43 (0.3)</td>
<td>19 (0.2)</td>
<td>24 (1.0)</td>
<td></td>
</tr>
<tr>
<td>Disease progressed/new primary</td>
<td>1274 (9.3)</td>
<td>994 (8.8)</td>
<td>280 (11.5)</td>
<td></td>
</tr>
<tr>
<td>Never started</td>
<td>245 (1.8)</td>
<td>208 (1.8)</td>
<td>37 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Other disease</td>
<td>56 (0.4)</td>
<td>46 (0.4)</td>
<td>10 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Other therapy</td>
<td>84 (0.6)</td>
<td>71 (0.6)</td>
<td>13 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Other/Missing</td>
<td>2053 (14.9)</td>
<td>1517 (13.4)</td>
<td>536 (22.1)</td>
<td></td>
</tr>
<tr>
<td>Refused further treatment</td>
<td>616 (4.5)</td>
<td>494 (4.4)</td>
<td>122 (5.0)</td>
<td></td>
</tr>
</tbody>
</table>

*a excluding NCCTG 89-30-52, CALGB 8541, CALGB 9344, and CALGB 9342 where this information was not available

*b excluding CALGB 9342 where this information was not available

*Note: 22 deaths were in the metastatic setting and 65% of pts in neoadjuvant setting were other/missing for reason

*In adjuvant setting: 80.1% younger pts completed tx as planned vs. 77.4 in age 65+
Summary and Implications

• We observed small increases in accrual of older patients to adjuvant trials but a decrease in accrual to trials in the neoadjuvant and metastatic setting.

• Overall, the proportion of patients enrolling to clinical trials age ≥65 and ≥70 remained low throughout the study period, with the exception of rare, selected trials:
  – i.e. 40% of all breast cancer occurs in age 65+ but only 20% and 10% of accruals were for ages 65+ and 70+.

• In general, % of older adults on neoadjuvant/metastatic trials was numerically higher than adjuvant trials, perhaps because of higher disease burden or symptomatic state:
  – Older patients on adjuvant studies had more nodal involvement → perhaps a higher threshold to treat
Summary and Implications

• We observed small increases in accrual of older patients to adjuvant trials but a decrease in accrual of older patients in the neoadjuvant and metastatic settings.

• Overall, the proportion of patients enrolling in clinical trials age ≥65 and ≥70 remained low throughout the study period, with the exception of rare, selected trials – i.e. 40% of all breast cancer occurs in age 65+ but only 20% and 10% of accruals were for ages 65+ and 70+.

• In general, the proportion of older adults on neoadjuvant/metastatic trials is higher than in the adjuvant setting, perhaps because of higher disease burden or symptomatic state.

• Older patients on adjuvant studies had more nodal involvement → perhaps a higher threshold to treat.
Study Limitations

• No information on the numbers of women approached, not approached, and why patients did not enroll on studies
• Analyses limited to Alliance Trials only
• We did not have complete disease characteristics, ECOG PS for some trials
Next Steps

• Poster presentation at ASCO 2016
• Paper in progress
• Draft to co-authors soon
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