A Decade of Breast Cancer Clinical Investigation: Results as Reported in the Program/Proceedings of the American Society of Clinical Oncology

by Rowan T. Chlebowski and Linda M. Lillington

Purpose: To test the hypothesis that clinical research results have driven changes in recent breast cancer management recommendations.

Methods: All breast cancer abstracts in the Program/Proceedings of the American Society of Clinical Oncology (ASCO) from 1984 to 1993 were prospectively reviewed in 31 areas and categorized by study type, study questions, whether statistical significance was claimed, and whether the abstract was presented.

Results: Of 1,372 abstracts, 54% reported on prospective clinical trials (PCTs) and 17% on randomized clinical trials (RCTs). The total number of published abstracts progressively increased (from 87 in 1984 to 221 in 1993) and abstract citations nearly quadrupled (from 430 in 1984 to 1,642 in 1993, P < .01); however, RCTs have come to represent a smaller proportion of reports: 37% (33 of 89) in 1986 versus 10% (22 of 221) in 1993 (P < .001). The size of adjuvant-therapy RCTs has progressively increased (mean ± SEM subjects/trial: 237 ± 43 in 1984 to 574 ± 374 in 1993), but has remained small in advanced-disease RCTs (mean ± SEM subjects/trial: 145 ± 25 in 1984 to 146 ± 34 in 1993). For adjuvant therapy, 14 of 90 RCTs (with 51,207 patients) reported a significant (P < .05) survival benefit for investigational therapies (16%). For advanced-disease therapy, only three of 141 RCTs (28,281 patients) reported a significant (P < .05) survival benefit for investigational therapies (2%). Randomization was rarely used in trials of dose-intensity with blood-product support (zero of 86 trials) or locally advanced disease.

Conclusion: For breast cancer ASCO abstracts in the past decade, we determined the following: (1) adjuvant trials have not infrequently supported study hypotheses; and (2) advanced-disease trials have consistently failed to identify new approaches with a significant impact on survival. These results suggest that a critical process evaluation of current policy and procedures involved in directing breast cancer research is warranted, especially for strategies in advanced disease.


METHODS

Abstracts published during the most recent 10-year period, including 1994 through 1993, were reviewed for content in 31 prospectively determined categories by one investigator (R.T.C.). The categories for review were determined by concurrence of a three-person expert panel of medical oncologists; the information collected is listed in Table 1. Abstracts were categorized by study category (prospective clinical trial, analytic study, nonclinical), study questions, whether statistical significance was claimed, and whether the abstract was selected for presentation.

The following definitions were used to categorize abstract reports: prospective clinical trials (PCTs) must have had a clearly defined prospective intervention not involving review of prior experience; randomized clinical trials (RCTs) must have additionally included the term randomization in the title or body of the abstract and must have incorporated two or more identifiable treatment arms. Analytic (cohort) studies involved either a prospective or a retrospective re-

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Table 1. Information Collected From ASCO Breast Cancer Reports

<table>
<thead>
<tr>
<th>Year</th>
<th>Abstract D</th>
<th>No. of authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institution: USA</td>
<td>Abstract Not USA-based</td>
<td></td>
</tr>
<tr>
<td>No. of patients reported in abstract</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Study category

I. Prospective clinical trial
   a) Multicenter
   b) Randomized
   c) Therapy category:
      Advanced disease
      Adjunctive
      Locally advanced
   d) Other
II. Analysis/review study
   a) Prospective
   b) Retrospective
III. Nonclinical study

Study question

I. New drug
   a) Chemotherapy
   b) Hormone therapy
II. Chemotherapy discontinuation
   a) With blood product support (bone marrow/stem cell)
   b) Without blood product support
III. Prognostic factors
IV. Comparison of regimens
V. Statistical difference claimed in abstract

On disease-free interval (in adjuvant trials)

II. On response or disease-free interval (in adjuvant trials)

III. On survival

Selected for presentation

A view of the patient population, often used to identify prognostic factors, or reviews of institutional treatment experiences. Chemotherapy dose-intensity studies with blood-product support must have included reference to either bone marrow transplantation or prospective harvesting and subsequent infusion of stem cells. Studies in locally advanced disease must have included either that phase or reference to therapy of stage IIIIB disease.

All abstracts listed in the breast cancer section, as well as those included under the topic of breast cancer in the ASCO Proceedings, were reviewed and are the subject of this report, with additional attention given to those reporting on PCTs. For all parameters, descriptive summary information was calculated (frequency, percentages, mean, and range). Comparisons between identified groups were determined by \( x^2 \) analyses and paired t-tests using the BMDP statistical software program.

RESULTS

A total of 1,372 abstracts published in the ASCO Proceedings between 1984 and 1993 were identified as pertinent to breast cancer. The majority (54%) of abstracts were reports of PCTs, with RCTs accounting for 17% of all reports (Table 2). The worldwide scope of the ASCO Proceedings was reflected in the representation of both United States-based (54%) and non-United States-based (46%) investigative teams reporting breast cancer studies as a relatively constant percentage throughout this period.

Table 2. ASCO Breast Cancer Reports (1984-1993) by Study Category

<table>
<thead>
<tr>
<th>Abstract Category</th>
<th>Total Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer as topic</td>
<td>1,372</td>
</tr>
<tr>
<td>PCTs</td>
<td>741</td>
</tr>
<tr>
<td>RCTs (total)</td>
<td>236</td>
</tr>
<tr>
<td>Total no. of patients entered or randomized trials (by category)</td>
<td></td>
</tr>
<tr>
<td>Advanced disease therapy</td>
<td>141</td>
</tr>
<tr>
<td>Adjunctive therapy</td>
<td>93</td>
</tr>
<tr>
<td>Total no. of patients entered on randomized trials by category</td>
<td></td>
</tr>
<tr>
<td>Advanced disease therapy</td>
<td>51,207</td>
</tr>
<tr>
<td>Adjunctive therapy</td>
<td>26,091</td>
</tr>
</tbody>
</table>

The number of total abstracts, those reporting on PCTs, and those reporting on RCTs on an annual basis over the past 10 years are graphically depicted in Fig 1. The number of published breast cancer abstracts progressively increased throughout the decade of review, with major increases occurring in 1988 and 1992. The mean number of authors per abstract has almost steadily increased as well, from 5.3 ± 0.21 (mean ± SEM) authors in 1984 to 7.43 ± 0.32 authors in 1993 (P < .01). Consequently, the number of authors of breast cancer reports in the ASCO Proceedings has nearly quadrupled from 430 in 1984 to 1,642 in 1993 (P < .01).
PCTs represented approximately half of all abstract reports. However, as the absolute number of abstracts reporting RCTs has remained constant, RCTs have become an increasingly smaller proportion of all ASCO breast cancer reports. RCTs represented 37% (33 of 89) of 1996 breast cancer abstracts, but only 10% (22 of 221) of 1993 breast cancer abstracts (P < .001). Single-institution reports of PCTs were consistently less likely to be randomized trials when compared with multisite reports throughout this period (18% vs 84%, respectively; P < .01).

The number of breast cancer abstracts selected for presentation at the ASCO Annual Meeting also increased during this time from 24 in 1984 to 23 in 1993, which reflects mainly a recent increase in poster presentations. The percentage of abstracts selected for presentation by abstract category is listed in Table 3. Throughout this period, PCTs were more likely to be selected for presentation at ASCO if they reported on randomized compared with nonrandomized trials (54% vs 17%, respectively; P < .05), and were especially likely to be selected if they reported a significant difference between treatments (69% presented). PCT reports selected for presentation were also nearly four times larger than those not presented (mean patient number, 272 ± 39 vs 75 ± 24, respectively; P < .05).

The randomized trials reported in the ASCO Proceedings, segregated on the basis of study type (adjuvant therapy vs therapy for advanced disease), as well as whether statistical significance was claimed for relapse-free survival (adjuvant), response frequency (advanced disease), and/or overall survival (both adjuvant and advanced), are listed in Table 4. Duplicate abstracts (reports or updates of the same study) were unusual (with the exception of one community-based report on the same cohort of patients treated with a breast-sparing approach, which was reported in 7 separate years). Almost no randomized PCTs with negative results were represented by more than one abstract report. Table 4 has been adjusted to reflect the two adjuvant trials with significant differences between treatment groups that were reported in more than 1 year (resulting in a total of five abstract reports on the two trials in the 10-year period). The earliest report, that indicated a significant difference between treatment groups in these two trials are included in Table 4.

Of 90 RCT's reporting on adjuvant breast cancer therapy, a statistical difference in relapse-free survival was reported in 32 (36%). Fifteen abstracts reported a statistically significant survival benefit as well. The abstracts that reported significant survival differences were clustered in the most recent years (with only two such reports before 1989) and appeared to represent both larger adjuvant trial sample sizes and longer follow-up periods. When the individual studies that claimed a statistically significant survival benefit for adjuvant treatment are considered, the investigational arm was found to be superior to either no treatment (three trials) or standard treatment (12 trials) in 14 of 15 cases. Thus, in 16% (14 intervention arms better than standard therapy or no therapy/control arms in 90 total trials) of ASCO reports of RCT in adjuvant breast cancer, the proposed hypotheses was supported as manifested by a statistically significant influence on survival.

<table>
<thead>
<tr>
<th>Abstract Category</th>
<th>% Selected for Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer, total reports</td>
<td>26</td>
</tr>
<tr>
<td>United States-based reports</td>
<td>23</td>
</tr>
<tr>
<td>Non-United States-based reports</td>
<td>29</td>
</tr>
<tr>
<td>PCTs, total</td>
<td>29</td>
</tr>
<tr>
<td>Randomized</td>
<td>17</td>
</tr>
<tr>
<td>Randomized with significant differences</td>
<td>69</td>
</tr>
</tbody>
</table>

Average no. of patients on PCT by abstract category:
- Not selected for presentation: 75 ± 24
- Selected for presentation: 272 ± 39

*P < .05 vs percent of total abstracts presented.

Table 4. ASCO Breast Cancer Reports (1984-1993) of RCTs by Category of Therapy and Trial Outcome

<table>
<thead>
<tr>
<th>Category</th>
<th>Adjunctive Therapy</th>
<th>Advanced Disease Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of RCTs</td>
<td>No. of Reports With Significantly Improved</td>
<td>Overall Survival</td>
</tr>
<tr>
<td>1984</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>1985</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>1986</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>1987</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>1988</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>1989</td>
<td>2</td>
<td>1</td>
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<tr>
<td>1990</td>
<td>11</td>
<td>4</td>
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<tr>
<td>1991</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>1992</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>1993</td>
<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>

Totals | 95 | 12 | 15

*Investigational therapy better than standard therapy in 3 trials (of 90 total trials, 16%). Two adjunctive trials were reported more than once during this period and only the initial report is included.

Investigational therapy better than standard therapy in 3 trials (of 14 total trials, 21%).

1994 | 16 | 2 | 2
Table 5. ASCO Breast Cancer Reports [1984-1993]: RCTs in Patients With Advanced Disease With Significant Difference in Survival Between Treatment Groups

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of Patients</th>
<th>Study Question</th>
<th>Summary Outcome</th>
<th>Response Frequency</th>
<th>Survival (months)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1984</td>
<td>273</td>
<td>CMF vs levamisole</td>
<td>Levamisole worse</td>
<td>FAC vs worse</td>
<td>20 vs 15</td>
<td>.01</td>
</tr>
<tr>
<td>1984</td>
<td>273</td>
<td>FAC before, during, after tamoxifen</td>
<td>FAC after worse</td>
<td>35 mg/m² vs worse</td>
<td>26 vs 21</td>
<td>&lt;.03</td>
</tr>
<tr>
<td>1984</td>
<td>273</td>
<td>A 70 mg/m² v 35 mg/m²</td>
<td>35 mg/m² worse</td>
<td>35 mg/m² vs worse</td>
<td>70 vs 8</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>1987</td>
<td>135</td>
<td>CMF high v low</td>
<td>Low worse</td>
<td>Low vs worse</td>
<td>16 vs 12</td>
<td>.01</td>
</tr>
<tr>
<td>1987</td>
<td>135</td>
<td>Tamoxifen v Megace</td>
<td>Megace worse</td>
<td>Megace vs worse</td>
<td>28 vs 20</td>
<td>.01</td>
</tr>
<tr>
<td>1987</td>
<td>135</td>
<td>Megace (standard v high) 100 mg v 1,000 mg</td>
<td>High better</td>
<td>Megace vs 1,000 mg</td>
<td>18 vs 11</td>
<td>.01</td>
</tr>
<tr>
<td>1990</td>
<td>127</td>
<td>RT oophorectomy ± prednisone</td>
<td>Prednisone better</td>
<td>Prednisone vs 27</td>
<td>Yes</td>
<td>.01</td>
</tr>
<tr>
<td>1991</td>
<td>127</td>
<td>Tamoxifen v Provera</td>
<td>Provera better</td>
<td>Provera vs 27</td>
<td>Yes</td>
<td>.02</td>
</tr>
<tr>
<td>1991</td>
<td>127</td>
<td>FEC every 4 weeks (standard v every week</td>
<td>Every-week schedule worse</td>
<td>Every-week vs 27</td>
<td>Yes</td>
<td>.02</td>
</tr>
<tr>
<td>1991</td>
<td>127</td>
<td>Megace (standard v high) 100 mg v 800 mg v 1,000 mg</td>
<td>No difference</td>
<td>Megace vs 27</td>
<td>NS</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviations: A, doxorubicin; C, cyclophosphamide; E, epirubicin; M, methotrexate; F, fluorouracil; P, prednisone; RT, radiation therapy; NS, not significant; Megace, megestrol acetate [Bristol-Myers, Princeton, NJ].

*Comparative survival, in months with P values; comparative response rates at percent total response frequency with P values. Not all information provided in all abstract reports.
†See 1992 report that unsuccessfully attempted to confirm result.
‡Trials in which investigational therapy resulted in significant survival benefit compared with standard therapy.

The results reported in the ASCO Proceedings of randomized trials in advanced breast cancer provide a striking contrast to the adjuvant experience. Of 141 randomized prospective trials in patients with advanced breast cancer, a statistically significant influence on response frequency was reported in 18 instances (13%). More importantly, only nine trials identified statistically significant differences in survival between treatment arms. The advanced-disease trials that reported a significant difference in survival are listed in Table 5. The response frequency in the arm with decreased survival was less than 29% in all but one study. In five of nine reports, the standard-therapy rather than the investigational-therapy group was reported to have a significant increase in survival. For example, levamisole plus cyclophosphamide, methotrexate, fluorouracil, vincristine, and prednisone (CMFVP) was associated with shorter survival than was CMFVP alone (standard); megestrol acetate was worse than tamoxifen (standard); low-dose cyclophosphamide, methotrexate, and fluorouracil (CMF) was worse than full-dose CMF (standard), etc.13,14 Of the remaining four reports, one identified a survival benefit for high-dose compared with standard-dose megestrol acetate,15 a result that was not supported in a much larger trial that addressed the same question and was subsequently reported at ASCO in 1992.16 Thus, in only 2% (three of 141) of randomized trials in advanced breast cancer reported in the ASCO Proceedings in the past decade has the proposed hypothesis been supported by a demonstration of a statistically significant influence on survival for the investigational treatment.

The three randomized studies in advanced breast cancer that reported a survival benefit for the investigational arm in the past 10 years in the ASCO Proceedings included the following: prednisone addition to oophorectomy alone in a randomized trial;17 me-droxyprogesterone acetate (Provera; The Upjohn Co., Kalamazoo, MI) superior to tamoxifen18, and tamoxifen plus concurrent fluorouracil, doxorubicin, and cyclophosphamide (FAC) superior to tamoxifen and delayed FAC chemotherapyy.19 The latter represents the only report with a significant survival difference involving chemotherapy (a total of 87 randomized chemotherapy trials) for patients with metastatic breast cancer.

Trends in the size of breast cancer clinical trials, as reflected by the average number of patients entered on randomized trials by year and study type (adjuvant advanced), are outlined in Fig 2. The average sample size of trials of adjuvant therapy has progressively increased (from 237 ± 43 in 1984 to 874 ± 371 in 1993; mean ± SEM), while the average size of trials in advanced disease has not changed during this period (from 145 ± 25 in 1984 to 146 ± 34 in 1993; mean ± SEM). In terms of total number of patients on randomized trials reported 1984.
A DECADE OF ASCO BREAST CANCER RESEARCH

Fig 2. Average number of patients entered per randomized clinical trial by year and study type (adjuvant vs advanced).

ASC0, in advanced disease trials 20% fewer patients were reported in 1993 compared with 1984 (trials included 2,304 patients in 1984 and included 1,885 patients in 1993, respectively), while in adjuvant trials a fourfold increase has occurred (adjuvant trials included 1,896 patients in 1984 and included 7,866 patients in 1993, respectively).

Trials of chemotherapy dose-intensity and those involving locally advanced breast cancer that were reported in the ASCO Proceedings rarely use randomized study designs. None of the 86 PCTs of dose-intensity that included blood-product support (bone marrow transplantation or re-infusion of harvested stem cells) and were reported in the ASCO Proceedings in this interval were randomized. In the last 3 years alone, 64 separate abstracts have reported on 1,956 breast cancer patients who were treated with high-dose therapy with blood-product support in nonrandomized trials. For locally advanced disease in the same 3-year period, 30 abstracts have reported on PCTs involving 1,477 breast cancer patients, two of which were randomized and included a total of only 37 patients.

Finally, use of the described methodology to review the most recent 1994 ASCO Proceedings generates similar results: 232 breast cancer abstracts were published with significant survival benefit reported in no RCTs of advanced disease but one RCT of adjuvant treatment.

DISCUSSION

The outcome of clinical investigations reported in the ASCO Proceedings has been favorable for investigational adjuvant breast cancer therapy. Not only have nearly 35% of trials reported relapse-free survival improvement, but more than 16% have reported a statistically significant impact on survival as well. Although apparently contradictory results raise some concerns, taken in total, these results suggest a well-founded basis for hypothesis formulation in adjuvant breast cancer trials, with the size of patient populations entered on studies reasonably based on achievable therapeutic differences.

For therapy of patients with advanced breast cancer, a different picture emerges. The 26,281 women reported in advanced breast cancer RCTs in the ASCO Proceedings in the past decade have provided surprisingly limited direction for clinical breast cancer management. In only three of 141 randomized PCTs in advanced breast cancer has the investigational arm demonstrated a statistically significant survival benefit compared with standard therapy. In two of these abstracts, which reported benefit for the new therapy, the standard therapy (of oophorectomy and tamoxifen, respectively) had surprisingly low response frequencies (27% and 15%, respectively), which suggests that chance rather than clinical efficacy may have dictated results. These results are disappointing, since, in many instances, similar hypotheses have been under evaluation in adjuvant and advanced breast cancer settings. Nonetheless, such negative results suggest that the experimental basis for bringing forward hypotheses to test in patients with advanced breast cancer may be inappropriate. It is more likely that the limited average number of patients entered on such trials has been too small to identify the type of differences in survival that can reasonably be anticipated based on the extensive clinical experience available in this area.

In any event, the decade of clinical investigation represented by publications in the ASCO Proceedings has failed to provide definitive information in support of new management approaches for breast cancer patients with advanced disease. The recognized difficulty of demonstrating a survival benefit when many therapies are compared in patients with advanced breast cancer has focused attention on the use of new criteria for end-point evaluation, including the use of quality-of-life indices. However, to date, reliance on such end points to assess breast cancer trials has only rarely been reflected in ASCO reports.

For future advanced breast cancer trials, the sample size issue will most likely become more prominent as breast cancer patients who present today for advanced...
breast cancer trials commonly have received adjuvant chemotherapy. Emerging data indicate that response rates to chemotherapy regimens for patients who fail to respond to adjuvant therapy are approximately half those seen in previously untreated patients.\(^5\) In addition, recent data suggest that prior adjuvant chemotherapy may lead to recurrence in harder-to-treat sites.\(^9\) The expectation for reduced response frequencies for breast cancer patients who relapse following adjuvant treatment, and the corresponding need for larger study populations, has not been reflected in recently reported advanced breast cancer clinical trials in the ASCO Proceedings. In this context, the factors that influence the increasing reliance on nonrandomized study designs in contemporary breast cancer clinical investigation for advanced disease trials also warrant attention.

Two areas of increasing clinical interest in breast cancer patient management have been underrepresented by randomized trials in the ASCO Proceedings in the past decade: locally advanced breast cancer and dose-intensity with blood-product support. Over the past 3 years, despite experience with 1,954 breast cancer patients in 64 reports on trials of dose-intensity involving blood-product support, the absence of randomized trials precludes definitive comparison of high-dose to conventional treatment. Nonetheless, based on the published cost for transplantation during this interval of approximately $100,000 per patient,\(^3\) these efforts have involved approximately $200,000,000 in patient care/research expenditure. It should be noted that randomized trials of this question are now underway. However, the question of the most appropriate time to initiate phase III testing of new and expensive technology remains, especially given the reimbursement issues,\(^2\) associated with this area. A somewhat similar situation holds in the area of locally advanced breast cancer management, where the absence in recent years of large randomized trials continues to leave major questions unanswered.

In summary, prospective review of breast cancer abstracts published in the Proceedings of the ASCO for the past decade indicates the following: (1) randomized trials have come to represent a decreasing proportion of ASCO abstract reports during this period; (2) trials of adjuvant breast cancer therapy have become progressively larger and not infrequently (in 16% of cases) support study hypotheses by demonstrating survival benefit for the investigational therapy under evaluation; and (3) trials of advanced breast cancer therapy have remained relatively small and have consistently failed to support study hypotheses or identify successful new management approaches as defined by a significant impact on patient survival.

Any recommendations based on these observations must recognize the complex nature of the clinical, scientific, and political issues surrounding breast cancer clinical investigation.\(^8\) Nonetheless, the presented data suggest several questions. Is it prudent, or even ethical, to continue to conduct clinical trials in advanced breast cancer populations based on demonstrably unreasonable assumptions of the anticipated magnitude of benefit? What is the benefit to the clinical and scientific community of publishing an ever-increasing number of clinical breast cancer abstracts in the ASCO Proceedings? Could this policy and/or the recognized problems of clinical cancer researchers\(^8\) be associated with some of the study design questions raised (such as encouraging small study populations)? Does current multisite clinical research policy appear to be designed to maintain patient recruitment (which often results in new protocols being opened as soon as accrual to prior studies is completed) foster an environment that diversifies clinical investigators from the results of their prior studies? Such questions and the need to conduct better breast cancer trials (larger in size and based on supportable hypotheses) lead to one recommendation: a critical process evaluation should be conducted of the policy and procedures associated with funding and conduct of breast cancer clinical investigation, especially in the advanced-disease area. As new agents are beginning to be evaluated in breast cancer clinical trials, lessons derived from the past could prove useful to define more effective evaluative strategies for the future.

REFERENCES

1. Editorial: Breast cancer: Have we lost our way? Cancer 34:133, 1973


