Facilitating consensus by examining patterns of treatment effects

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Original Article

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Summary

Randomized clinical trials are necessary to provide reliable evidence concerning the effectiveness and safety of adjuvant therapies for breast cancer. Such trials, however, are not sufficient to provide information needed to tailor therapies to individual patients. Trials focus on testing treatments on average for heterogeneous patient populations, while attention to the specific characteristics of the disease and the patient are needed to assess the potential benefit for the individual. While ‘across the board’ results are useful from a population perspective, examination of patterns of treatment response during the course of follow up and for subpopulations of patients is required to make progress and solidify consensus on how to treat individual patients. For example, for several decades it has been known that the pattern of recurrence risk from time of diagnosis is different for estrogen receptor (ER)-negative and ER-positive disease. Assuming that ER status is accurately assessed and distinguishing absence of receptors from low, intermediate and high expression cohorts, one can recognize patterns of relapse risk that are early versus later during follow up. Treatments effective against ER-negative disease reduce the risk of early relapse, while those acting on ER-positive disease demonstrate effectiveness later during the course of follow up. Another example is HER2-positive disease, where a relatively high proportion of patients tend to relapse early, and treatments such as trastuzumab that reduce the risk of early relapse have demonstrated efficacy. For premenopausal patients with ER-positive disease, ovarian function suppression and endocrine effects of chemotherapy are effective to reduce the risk of late occurring relapses. Examining the influence of patient and disease-related factors on the patterns of recurrence over time and treatment responsiveness within subpopulations in multiple randomized trials can facilitate consensus on progress that has been made and identify areas for improving the care of patients with breast cancer.

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Introduction

As the opening lecture at the 11th St. Gallen Conference on the Primary Therapy of Breast Cancer, in March 2009, this presentation provided a new lens for examining clinical trial results by describing different clinical scenarios focusing less on the treatments being studied and more on the population of patients. An additional goal was to assist the panelists in their deliberations on updating the 2007 St. Gallen treatment algorithm which had provided a guide for selecting adjuvant therapy modalities. The examination of the patterns of events in the control groups and treatment groups that occur at different periods over time and for different subpopulations provides a framework for interpretation of data. The era of “one size fits all” adjuvant therapy is being replaced by a more tailored, individualized approach to treatment selection.

Age is not a therapeutic target

In the past, age was considered an important criterion for determining chemotherapy administration. The Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) overview data shown in Fig. 1A supported the hypothesis that younger women derive more benefit from chemotherapy than older women. However, the differential magnitude of chemotherapy benefit might be associated with features related to age, rather than age per se. What happens to the patterns of treatment effects if a more patient and disease-focused approach is used to look at the data? For example, in Fig. 1B, only patients with estrogen receptor (ER)-poor disease (endocrine nonresponsive) are included and the difference in treatment benefit is not as striking as in Fig. 1A. In fact, some treatment benefit emerges for older patients, although restricting
### A. All patients

Recurrence/woman-years

<table>
<thead>
<tr>
<th>Entry age</th>
<th>Events/woman-years</th>
<th>Chemotherapy events</th>
<th>Ratio of annual event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Allocated control</td>
<td>Adjusted control</td>
<td>Logrank</td>
</tr>
<tr>
<td></td>
<td>chemotherapy</td>
<td></td>
<td>O-E</td>
</tr>
<tr>
<td>Age &lt;40</td>
<td>395/7077 (5.6%/y)</td>
<td>479/5595 (8.6%/y)</td>
<td>-88.7</td>
</tr>
<tr>
<td>40-49</td>
<td>832/19553 (4.3%/y)</td>
<td>1045/16629 (6.3%/y)</td>
<td>-174.9</td>
</tr>
<tr>
<td>50-59</td>
<td>1965/33600 (5.8%/y)</td>
<td>2389/31644 (7.5%/y)</td>
<td>-219.5</td>
</tr>
<tr>
<td>60-69</td>
<td>2004/31655 (6.3%/y)</td>
<td>2221/30332 (7.3%/y)</td>
<td>-112.9</td>
</tr>
<tr>
<td>&gt;70</td>
<td>194/3388 (5.7%/y)</td>
<td>253/3835 (6.6%/y)</td>
<td>-9.3</td>
</tr>
<tr>
<td>Age unknown</td>
<td>7/130</td>
<td>12/74</td>
<td>-1.4</td>
</tr>
</tbody>
</table>

**Fig. 1.** Event rate ratios for recurrence, polychemotherapy versus not according to age group: all patients (panel A, ref., 2 fig. 1; adapted with permission), ER-poor cohort (panel B, ref., 3 fig. 1; adapted with permission), and ER-poor cohort in the absence of tamoxifen in both treatment groups (panel C, ref., 3 fig. 1; adapted with permission).
the analysis to the ER-poor cohort reduces the amount of statistical information to 22% of the total available in Fig. 1A.

Few patients less than 50 years of age received tamoxifen and the positive effect of chemotherapy in this age group remains. Most patients 50 and above, enrolled in older trials, received tamoxifen even if the disease was ER-poor – 56% in the age group 50–59 and 72% in the age group 60–69. When the studies that included tamoxifen in both treatment groups were eliminated (Fig. 1C) women in their sixties appear likely to receive as much benefit from chemotherapy as women in their forties, if their disease is endocrine nonresponsive. Almost 90% of the statistical information has now been eliminated, but the pattern of outcomes that emerges clearly indicates that age is not a target for chemotherapy efficacy.

Accuracy of ER and HER2 determinations must improve

Obviously accurate assessment of biological markers is required in order to obtain clear signals of effects from targeted therapies. Between June 2007 and November 30, 2008, tumor blocks from almost 5000 patients with local determination of HER2-positive breast cancer were centrally reviewed at the pathology laboratory of the European Institute of Oncology (Prof. Giuseppe Viale, Director) for potential enrollment in the ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) trial.4 As of 30 November 2008, pre-randomization central review determined that 602 (13.7%) of the 4327 patients with locally determined HER2-positive disease (excluding cases with equivocal local determination) were not eligible to enter the ALTTO trial using criteria for trial eligibility based on the CAP/ASCO definition of HER2-positive.5 Pre-randomization central review of ER and progesterone receptor is also performed in the ALTTO study, and the results for ER status (local laboratory determination and European Institute of Oncology central review) are shown in Table 1 (G. Viale, personal communication). Of the 2648 cases determined to be locally positive, 4.3% had no expression of ER at central review, a false positive finding. Over 20% of the cases determined to be locally ER-negative had at least some ER expression on central review. Assuming that the central review provides a more accurate assessment of the true characteristics of the tumor than the local laboratory findings, using HER2 and ER values from local laboratories may lead to inappropriate selection of adjuvant therapies for many patients.

What evidence do we have that pathological assessments are more accurate if conducted in high volume, laboratories specializing in breast cancer phenotyping? The Viale laboratory in Milan also conducted central review for the Breast International Group (BIG) 1-98 trial – a study of letrozole versus tamoxifen for postmenopausal women with hormone receptor-positive disease.6,7 Central review identified 94 of 3610 patients (2.6%) with hormone receptor-negative disease who were randomized to receive tamoxifen or letrozole for five years.8 The pattern of disease recurrence for these false positive cases, shown in Fig. 2, is classic for an endocrine responsive disease – rapid early decline with a later plateau.9 By contrast, the true hormone receptor-positive cases have the endocrine responsive pattern – relapses occurring at a lower annual rate, but continuing for long follow up.

Patterns of chemotherapy effects for premenopausal women with endocrine-responsive breast cancer

International Breast Cancer Study Group (IBCSG) Trial 11-93 investigated whether four courses of anthracycline-based chemotherapy would provide additional efficacy to that of effective endocrine therapy – combined tamoxifen and ovarian function suppression – for premenopausal patients with node-positive disease.10,11 Between 1993 and 1998, only 174 patients, almost all with one to three positive nodes, entered the trial. The results for the two treatment groups in terms of disease-free survival (DFS) at ten years’ median follow up appear super imposable (Fig. 3). The role of adding chemotherapy for premenopausal women who receive appropriate endocrine therapy remains controversial.

Adjuvant! Online© is a useful program for providing individual patient estimates of improvement in relapse-free survival (RFS) and overall survival (OS) that might be achieved with a variety of treatment regimens.12,13 Baseline characteristics of patients enrolled in Trial 11-93 were entered into Adjuvant! Online and the resulting estimates of projected RFS were calculated and compared with the values generated directly from the Trial 11-93 data [manuscript in preparation].

Table 1

<table>
<thead>
<tr>
<th>ER Local lab</th>
<th>Central Review (European Institute of Oncology)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive ≥10%</td>
</tr>
<tr>
<td>Positive</td>
<td>2481</td>
</tr>
<tr>
<td>Negative</td>
<td>388 (16.9%)</td>
</tr>
</tbody>
</table>

4 With permission from ALTTO Executive Committee.
endocrine therapy alone estimated from Adjuvant! Online was significantly lower than the Trial 11-93 results. Trial 11-93 is the only randomized evidence directly evaluating the role of chemotherapy when added to optimal endocrine therapy for a highly endocrine-responsive, premenopausal population. Therefore estimates from Adjuvant! Online are based on information from indirect comparisons and may not be precise in this specific setting.

In fact, the Austrian Breast Cancer Study Group (ABCSG) Trial 12\(^{14}\) also showed excellent results for premenopausal women with endocrine-responsive disease who did not receive adjuvant chemotherapy. In this trial with 33% of the patients having node-positive disease, overall 4-year disease-free survival (DFS) was 92%, indicating that all patients received very effective endocrine adjuvant treatment – ovarian function suppression (OFS) plus tamoxifen or anastrozole for the duration of three (3) years. Assessing the worth of aromatase inhibitors in this setting requires longer follow up and we await completion of the ongoing Tamoxifen and Exemestane Trial (TEXT) study which evaluates five (5) years of OFS with triptorelin and either tamoxifen or exemestone.\(^{15,16}\)

The presentation of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-30 study at the San Antonio Breast Cancer Symposium (SABCS) in December, 2008,\(^{17}\) provided additional evidence supporting the role of chemotherapy-induced amenorrhea as a factor to improve outcome for premenopausal women with endocrine-responsive disease. Three taxane containing regimens were compared across the board for patients with node-positive disease. The study enrolled 5351 women. The population was relatively lower risk; two-thirds had 1–3 positive axillary lymph nodes, three-quarters had ER-positive disease, and about half were premenopausal. At 73 months of median follow up, the pattern of events over time is consistent with what would be expected for this population. The longer duration, sequential therapy, AC followed by docetaxel, demonstrated improved disease-free survival compared with the shorter duration regimens in which anthracycline and taxane were given concurrently. The difference in disease-free survival between premenopausal women who developed chemotherapy-induced amenorrhea and those who did not have amenorrhea was much greater that the difference in outcomes according to randomized treatment. The amenorrhea effect was largest for the longer duration treatment. The recurrences occur over time and the curves continue to diverge with longer follow up – an endocrine-related pattern. This new information provides additional indirect evidence supporting the therapeutic advantage of ovarian function suppression – a hypothesis being directly tested in the ongoing Suppression of Ovarian Function Trial (SOFT) study.\(^{15}\)

Patterns of trastuzumab effects for HER2-positive breast cancer

The HERA trial, one of several large randomized studies evaluating the efficacy of trastuzumab for HER2-positive disease reported in 2005, demonstrated substantial improvement in DFS and OS.\(^{18}\) Previous subgroup analyses showed that trastuzumab was effective across the board – in particular, average treatment benefit was the same for patients with endocrine nonresponsive and endocrine-responsive disease (Fig. 4A).\(^{19}\) However, the patterns of when during follow up the effects were seen for these two populations differed substantially. For patients with endocrine-responsive disease (Fig. 4B), the addition of trastuzumab to endocrine therapy improves outcome. With 2 years’ median follow up the Kaplan–Meier curves separate at about one year and the reduction in risk persisting as follow up continues.\(^{20}\) By contrast, for patients with HER2-positive, receptor-negative disease, the benefit of trastuzumab emerges very early with substantial reduction of the risk for early relapses (Fig. 4C).\(^{20}\) Whether this early benefit could be sustained by extending the duration of trastuzumab from 1 year to 2 years is being evaluated in the follow up of the HERA trial.\(^{20,19}\)

Patterns of chemotherapy effects according to HER2 and ER status

How do the positive results for trastuzumab in the HER2-positive cohort, and evidence of more effective endocrine therapies for patients with ER-positive disease affect our interpretation of chemotherapy results from other trials? Figure 5 shows the patterns of treatment effects reported by Dr. Daniel Hayes and colleagues from the CALGB trial 9344 of AC followed by paclitaxel versus AC alone for patients with node-positive disease.\(^{21}\) Four categories were identified based on central review for HER2, ER and PgR. The different patterns of events in the four AC control groups is quite interesting (Figs. 5A–5D). The HER2-positive groups are shown on the bottom – receptor negative on the left (Fig. 5C) and receptor positive on the right (Fig. 5D). The receptor negative, HER2-positive group treated with AC alone has a very rapid decline during the first three years and then a plateau (Fig. 5C). The recurrences that contribute to this early decline are precisely those that are avoided by use of trastuzumab in the HERA trial (Fig. 4C). For the HER2-positive, receptor positive group on the lower right (Fig. 5D), the pattern of benefit from adding the taxane is similar to the pattern seen for trastuzumab in HERA (Fig. 4B). The triple negative cohort shown on the upper left (Fig. 5A) obtains benefit from the taxane, but more improvement is needed. Finally, the HER2-negative, endocrine-responsive group on the upper right (Fig. 5B) (which includes both younger and older women) displays the slow but relentless pattern of recurrences characteristic for this group. Improving endocrine and targeted therapies is probably the best option for these women.

Patterns of bisphosphonate effects on breast cancer relapse

The Zo-FAST trial for postmenopausal women with endocrine-responsive disease evaluated immediate versus delayed use of zoledronic acid.\(^{22}\) All patients received letrozole. This study enrolled a low risk population of 1065 women, with over 92% of patients without an event within 3 years. Although the immediate zoledronic acid group had a 40% reduced risk of recurrence during the relatively short-term follow up of the trial, this result is based on a total of 62 events, 22 in the immediate and 40 in the delayed zoledronic acid group.

Similarly for premenopausal women, evidence of bisphosphonate effect on breast cancer recurrence is based on very few events within a low risk population studied. The ABCSG Trial 12,\(^{14}\) recruited 1803 women followed for 4 years, with 137 disease-free survival events recorded: 54 for women who received zoledronic acid and 83 for those who did not. Interestingly, the overall effect appears to be ‘driven’ almost exclusively by the results for women who received ovarian function suppression plus anastrozole for three years, with a modest effect for the tamoxifen treated group.\(^{23}\) This raises questions about widespread use of bisphosphonates for premenopausal women for whom tamoxifen is used outside of clinical trials.

Conclusion

Consensus for treatment guidelines can be facilitated by examining patterns in trial results, especially those replicated in multiple studies. Trialists should be strongly encouraged to collect biological material for central review and assessment of new predictive factors (e.g., pharmacogenetic studies and multigene expression assays). And individual patient variability, rather treatment for the average, should guide clinical trial design and analyses.
A. Hazard ratios according to hormone receptor status

<table>
<thead>
<tr>
<th>Subgroup (no. patients)</th>
<th>No. events</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T vs obs</td>
<td></td>
</tr>
<tr>
<td>ER negative + PgR negative (1627)</td>
<td>126 vs 190</td>
<td>0.63 (0.50, 0.78)</td>
</tr>
<tr>
<td>ER negative + PgR positive (172)</td>
<td>12 vs 12</td>
<td>0.77 (0.34, 1.74)</td>
</tr>
<tr>
<td>ER positive + PgR negative (460)</td>
<td>26 vs 39</td>
<td>0.82 (0.50, 1.34)</td>
</tr>
<tr>
<td>ER positive + PgR positive (984)</td>
<td>46 vs 61</td>
<td>0.63 (0.43, 0.93)</td>
</tr>
<tr>
<td>All patients (3401)</td>
<td>218 vs 321</td>
<td>0.64 (0.54, 0.76)</td>
</tr>
</tbody>
</table>

Favors Trastuzumab HR Favors observation

T, trastuzumab; obs, observation; HR, hazard ratio.

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**Fig. 4.** Hazard ratios (HR) for disease-free survival comparing one year of trastuzumab to observation for patients with HER2-positive breast cancer enrolled in the HERA trial at 2 years of median follow up (panel A) (ref.19 fig. 3; adapted with permission), and Kaplan–Meier plots (left side) and annualized hazard rates (right side) for disease-free survival for subgroups defined by steroid hormone receptor positive (ER and/or PgR-positive, panel B) or negative (ER and PgR-negative, panel C) (ref.20 fig. 2; reproduced with permission).

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**Competing interests:** Both authors have no competing interests to declare.
Fig. 5. Disease-free survival among patients treated with or without paclitaxel after completion of four cycles of doxorubicin and cyclophosphamide according to estrogen-receptor and HER2 expression in CALGB Trial 8541 (ref.21 fig. 2; reproduced with permission).

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4. Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation (ALTTO) trial. Website: alttotrials.com [last accessed 24 March 2009].


