Factors Used to Select Adjuvant Therapy of Breast Cancer in the United States: an Overview of Age, Race, and Socioeconomic Status

Hyman B. Muss

Age, race, and socioeconomic status all play a role in decisions regarding breast cancer adjuvant therapy. Increasing age remains the major risk factor for breast cancer, while in very young women breast cancer may have a poorer prognosis, even when adjusted for disease stage and other variables. More than half of all new breast cancers in the United States occur in women older than 65 years. Because of the higher frequency of coexisting (comorbid) serious illness in older women, the benefits of adjuvant therapy get smaller as age increases. Adjuvant therapy with tamoxifen and/or chemotherapy can statistically significantly improve survival in older women, but older women are less likely to receive chemotherapy and are less likely to be offered participation in clinical trials. Efforts are now under way to overcome age bias among health care providers and to develop clinical trials focusing on older patients. Breast cancer mortality is higher in African-Americans than in white Americans. Although the biologic characteristics of breast cancer are worse in African-Americans, major differences in survival are related to socioeconomic factors and access to care. When matched for disease stage and other major clinical and biologic variables, African-American and white patients have similar survival rates. Few data are available on the effects of adjuvant treatment on early breast cancer outcomes in Hispanic Americans and Asian-Americans. Poverty and lack of insurance are surrogates for poor outcomes; major efforts are needed to guarantee all Americans high-quality cancer care. [Monogr Natl Cancer Inst 2001;30:52–5]

Age, race, and socioeconomic status all affect decisions regarding breast cancer adjuvant therapy. More than half of all new breast cancers in the United States occur in women 65 years old or older, a statistic that has even more impact in a population whose longevity is increasing (1). Since coexisting illness (comorbidity) statistically significantly increases with age, it is a major factor in determining the relative benefit of adjuvant therapy on patient survival (2). In younger women, especially those less than 35 years old, breast cancer may have a poorer prognosis, even when adjusted for disease stage and other variables (3,4). African-Americans now constitute 12.7% of the U.S. population and have higher breast cancer mortality compared with Caucasian Americans, even after adjustment for disease stage (5). Such differences are related to several factors, including stage at presentation, tumor biology, and sociodemographic characteristics (5). Few data are available concerning breast cancer outcomes in Hispanic Americans who constitute 8.2% of the population, Asian-Americans who constitute 1.6% of the population, and Native Americans who constitute almost 1% of the population. In one study of 163 African-American, 205 Hispanic, and 964 Caucasian women, lower socioeconomic status was the major factor related to the poorer survival rates of Hispanic and African-American women compared with Caucasian women (6).

RACE AND SOCIOECONOMIC STATUS AS A FACTOR IN ADJUVANT THERAPY OF BREAST CANCER

Several trials have shown small but potentially important biologic differences in breast cancer among African-American and Caucasian patients. African-American patients are more likely than Caucasians to have more biologically aggressive tumors, including larger tumor size, an increased likelihood of involved lymph nodes, lack of hormone receptors, and a higher rate of tumor proliferation (Table 1) (7). Hispanic Americans had tumor characteristics somewhat worse than Caucasians but better than African-Americans in this series. These adverse biologic tumor characteristics may limit the potential life-prolonging benefits of tamoxifen therapy or ovarian ablation in African-American and Hispanic patients compared with Caucasians. In large numbers of patients, these small differences in tumor biology may prove to be highly meaningful.

African-Americans and Hispanics do appear to be adequately represented in clinical trials (8). Limited data suggest that, at least for African-Americans, the benefits of adjuvant therapy are similar to those for Caucasian women when outcomes are adjusted for disease stage, comorbid illness, and pathologic and sociodemographic variables (9,10); however, most studies have not had the power to adequately test whether specific treatments have different survival and response rates in minority populations compared with the study group as a whole. Few data are available on Hispanic patients and other minorities concerning the risks and benefits of adjuvant therapy. The data also suggest that for Hispanics, like African-Americans, socioeconomic factors play a key role in outcome (6).

Poverty is associated with poorer cancer outcomes for all Americans, irrespective of racial or ethnic group, and remains a national issue (11). In one sobering study of 4675 women aged 35–64 years with breast cancer entered in the New Jersey State Tumor Registry, the adjusted risk of death was 49% higher for uninsured patients and 40% higher for Medicaid patients than for privately insured patients during the 54–89 months after diagnosis, even after adjustment for age, race, household income, coexisting illness, and disease stage (12). These numbers are of major concern, since 40–50 million Americans are cur-

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See “Note” following “References.”

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Table 1. Differences in tumor biology among different racial and ethnic groups*  

<table>
<thead>
<tr>
<th></th>
<th>Caucasian, %</th>
<th>Hispanic, %</th>
<th>African-American, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, ≤50 y</td>
<td>23.9</td>
<td>32.0</td>
<td>37.4</td>
</tr>
<tr>
<td>Tumor size, &gt;2 cm</td>
<td>55.5</td>
<td>67.9</td>
<td>70.3</td>
</tr>
<tr>
<td>Lymph node positive</td>
<td>42.1</td>
<td>54.1</td>
<td>51.2</td>
</tr>
<tr>
<td>Estrogen receptor positive</td>
<td>56.0</td>
<td>50.6</td>
<td>40.8</td>
</tr>
<tr>
<td>High S phase</td>
<td>38.5</td>
<td>48.4</td>
<td>49.4</td>
</tr>
<tr>
<td>HER2+</td>
<td>16.1</td>
<td>20.9</td>
<td>13.8</td>
</tr>
</tbody>
</table>

*Thirty-one hospitals in the United States. Modified from Elledge et al. (7).  

Breast cancer biology changes with age, and older patients have more favorable tumor characteristics. Diab et al. (15) compared the tumor and biologic characteristics of breast cancer patients among age groups (Table 2). These more favorable tumor characteristics may translate into improved survival; for lymph node-negative patients in this series, survival was similar among breast cancer patients 70 years old or older and age-matched women from the general population. Nevertheless, several trials have shown that older women are less likely to receive appropriate local therapy, such as postoperative local radiation, or adjuvant systemic therapy compared with younger women (16). In healthier older women with higher risk lymph node-negative and lymph node-positive breast cancer, however, such undertreatment may lead to poorer outcomes.

Compelling data from a worldwide meta-analysis of adjuvant therapy (17) showed that, for older patients with estrogen receptor-positive or progesterone receptor-positive tumors, tamoxifen statistically significantly increased both relapse-free and overall survival. Women 70 years old or older who took tamoxifen for 5 years had a 54% decrease in the annual odds of breast cancer recurrence and a 34% decrease in the annual odds of dying of breast cancer. Chemotherapy alone has not been studied adequately in older patients; in the same overview, fewer than 700 women 70 years old or older were entered in randomized trials. Chemotherapy, however, was associated with statistically significant improvements in both relapse-free and overall survival in women aged 50–69 years (a 20.3% and 11.3% reduction in annual odds of relapse and death, respectively) (18). It is reasonable to expect that chemotherapy would have a similar effect in women 70 years old or older, but more data on chemotherapy trials are needed in older women.

The effects of major coexisting illness on survival are a crucial factor in assessing the potential benefits of chemotherapy in older patients. The potential benefits of adjuvant therapy in older women have been estimated recently with the use of a mathematical model (19); it is clear that the value of adjuvant therapy diminishes substantially as age and comorbidity increase and as survival in women 60 years old or older. Similar statistics are found in other industrialized countries. Since the populations of the United States and other industrialized nations continue to age, breast cancer is likely to be a more prevalent and common disease in the future (14) Goldhirsch et al. (4) in this monograph have presented compelling data that, for very young women, breast cancer carries a poorer prognosis even after adjustment for disease stage and other clinically important prognostic factors. Such data suggest that clinical trials in these young patients should explore more aggressive and, hopefully, more beneficial therapies than current standard treatments.

Table 2. Differences in tumor biology with increasing age*  

<table>
<thead>
<tr>
<th>Age, y</th>
<th>55–64</th>
<th>65–74</th>
<th>75–84</th>
<th>≥85</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>12101</td>
<td>13123</td>
<td>7873</td>
<td>2018</td>
</tr>
<tr>
<td>Lymph node negative, %</td>
<td>59</td>
<td>65</td>
<td>66</td>
<td>61</td>
</tr>
<tr>
<td>Estrogen receptor positive, %</td>
<td>83</td>
<td>87</td>
<td>90</td>
<td>91</td>
</tr>
<tr>
<td>Low S phase, %</td>
<td>51</td>
<td>57</td>
<td>61</td>
<td>60</td>
</tr>
<tr>
<td>HER2+, %</td>
<td>21</td>
<td>15</td>
<td>14</td>
<td>10</td>
</tr>
</tbody>
</table>

*All differences are statistically significant across groups (P<.001). Modified from Diab et al. (15).
non-breast cancer-related illness becomes a major competing cause for death. What is also clear is that older women in good general health tolerate standard chemotherapy regimens almost as well as younger women (20,21). Outside a trial, recommendations for adjuvant therapy made by an international consensus panel appear prudent and should be used as a treatment guideline (Table 3) (22).

Comorbidity is frequently a key issue in the decision to use adjuvant systemic therapy in the elderly. As comorbidity increases, the potential benefits of adjuvant therapy decrease, since the risk of dying of other non-breast cancer-related causes becomes more likely. In one study, women with three or more comorbid illnesses had a 20-fold higher risk of dying of non-breast cancer-related causes than women with no comorbid conditions, even after adjustment for disease stage, type of treatment, race, and social and behavioral factors (23). Several investigators (2,19,24) have developed models to predict the likely benefit of age or comorbidity on treatment outcome in older women with early-stage breast cancer. These models clearly show that the benefits of adjuvant therapy decrease with increasing age or comorbidity. Welch et al. (25) also provided data derived from a Markov model that predicted the effect of comorbidity on life expectancy (Fig. 2). Even with potentially curative treatment, the effect of such treatment on overall life expectancy would be small for very old patients.

It is clear that older patients are underrepresented in clinical trials (8,26). Hutchins et al. (8) analyzed data from 16,396 patients consecutively enrolled in 164 Southwest Oncology Group treatment trials during the period from 1993 to 1996. Only 9% of the patients entered in breast cancer clinical trials were 65 years old or older compared with population and census estimates that indicated 49% of women with breast cancer during this time period were 65 years or older (8). Barriers to the participation of older women in clinical trials have been well defined by Trimble et al. (26) and include the following: 1) a research focus on aggressive therapy, which may be unacceptably toxic to the elderly; 2) the presence of comorbidity; 3) fewer trials specifically aimed at older patients; 4) limited expectations for long-term benefits on the part of physicians, relatives, and the patients themselves; and 5) a lack of financial, logistic, and social support for the participation of elderly patients in clinical trials (26). Issues related to reimbursement may be partially overcome by the recent Presidential mandate to the Center for Medicare and Medicaid Services to reimburse the costs of routine care for patients entered in appropriately reviewed clinical trials. Moreover, a recent study from the Cancer and Leukemia Group B (27) compared participation in clinical trials among patients with stage I, II, or IV breast cancer who were less than 65 years with that among patients who were 65 years old or older who were treated by the same physician and who were eligible for a clinical trial within their institution. Of 77 pairs of patients matched on the basis of disease stage and treating physician, 34% of those 65 years old or older were offered trial participation compared with 51% younger than 65 years (P<.05). When participation in a trial was offered, however, similar rates of acceptance were found in the older and younger women (50% and 56% for older and younger women, respectively). Even after adjustment for other covariates, including race, comorbidity, educational level, marital status, and satisfaction with care, age alone predicted for a lower likelihood of being offered a clinical trial. Efforts are now under way to overcome these barriers and include National Cancer Institute and National Institute of Aging funding for clinical trials directed at older women (Table 4) (28).

**CONCLUSIONS**

Racial, ethnic, and aging issues play a major role in appropriate delivery of adjuvant therapy in women with early-stage breast cancer. Although there are differences in tumor biology related to age and race, the major issue related to adjuvant therapy is access to care. For African-American and other ethnic and racial groups, socioeconomic factors are far more important than biologic factors in determining outcome. Lower incomes, limited or absent insurance coverage, and poorer education all translate into less access to initial quality treatment and later on to poorer survival.

**Table 3. Recommendations for adjuvant therapy for women 70 years old or older**

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Size, ER status, grade</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node negative, low (&lt;10%)</td>
<td>≤1 cm, nonpalpable</td>
<td>None or Tam</td>
</tr>
<tr>
<td>Lymph node negative, intermediate (10%–15%)</td>
<td>&gt;1 ≤2 cm, ER+, grade I or II</td>
<td>Tam ± Chemo</td>
</tr>
<tr>
<td>Lymph node negative, high (&gt;15%)</td>
<td>&gt;1 cm and ER− or &gt;2 cm and ER+ or grade III</td>
<td>Tam and/or Chemo if tolerated</td>
</tr>
<tr>
<td>Lymph node positive</td>
<td>ER+ or PR+</td>
<td>Tam</td>
</tr>
<tr>
<td></td>
<td>ER− and PR−</td>
<td>Chemo</td>
</tr>
</tbody>
</table>

*From Goldhirsch et al. (22). ER = estrogen receptor. Tam = tamoxifen; Chemo = chemotherapy.
Efforts are needed to provide all Americans with access to quality medical care. The survival benefits of systemic adjuvant therapy in early breast cancer are undisputed, and these treatments should be available to all Americans. Research is needed to determine the molecular mechanisms that underlie the differences in tumor biology among diverse racial and ethnic groups. For older Americans, research is needed on the interactions of adjuvant therapy and coexisting illness and how such interactions affect quality of life, activities of daily living, and survival. Moreover, education of physicians and the public concerning issues related to cancer in older patients is necessary to overcome age bias in treatment selection.

REFERENCES


NOTE

H. M. Muss is a consultant for AstraZeneca; has received research funding from Aventis, AstraZeneca, Genentech, Bristol-Myers-Squibb, Ortho-Biotech, Novartis, and the Genetics Institute; has received fellowship support from Amgen; and has received honoraria from AstraZeneca and the Network for Oncology Communications.