

## Adjuvant Treatment of Breast Cancer in Older Patients

a report by

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Breast cancer is a disease associated with aging, and the majority of deaths from breast cancer occur in women over the age of 65.<sup>1</sup> The literature to date reports significant variations in patterns of care, with older patients less likely to receive breast-conserving surgery, radiation, and adjuvant chemotherapy.<sup>2-9</sup> In addition, there is a disproportionately lower enrolment of older adults in breast cancer clinical trials, on which the standards for oncology care are based.<sup>10,11</sup> Therefore, the rationale for commonly offered treatments is based on the results of studies of almost exclusively younger populations; and for oncologists, there is little research to guide their decisions regarding the benefits and risks of various treatment modalities for older patients. In this article the available data concerning the treatment of early-stage breast cancer in older adults are discussed and future research directions are proposed.

Surgery is the primary treatment of choice in early-stage breast cancer for patients of all ages. Older patients who do not undergo surgical removal of the tumor are at increased risk for breast cancer progression and mortality. This was demonstrated in a study of 455 women over the age of 70 who had operable, invasive breast cancer and who were randomized to receive either tamoxifen alone or surgery plus tamoxifen. The elimination of surgery was associated with a statistically significant increased risk of breast cancer mortality.<sup>12</sup> A more recently published Cochrane review evaluated six trials of women over the age of 70. The review demonstrated an improvement in progression-free survival in patients who received surgery plus endocrine therapy compared with endocrine therapy alone, although no difference in overall survival was seen.<sup>13</sup>

Radiation therapy is usually given after breast-conserving surgery to decrease the risk of a local recurrence. A trial designed by the Cancer and Leukemia Group B (CALGB) evaluated the question of whether radiation therapy could be eliminated in older women with stage I hormone-receptor-positive breast cancer. In this study, patients aged 70 and older with clinical stage I hormone-receptor-positive disease were randomized to either lumpectomy and radiation therapy or lumpectomy alone. All

patients received tamoxifen. The elimination of radiation therapy was associated with an increased risk of a local recurrence (4 versus 1%;  $p < 0.001$ ); however, there was no difference in distant metastases or five-year overall survival.<sup>14</sup> In contrast, observational data from the Surveillance, Epidemiology, and End-Results (SEER) Medicare database demonstrates that for patients age 70 and older with high risk (T3/4 or

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N2/3) breast cancer, the receipt of post-mastectomy radiation therapy is associated with a survival benefit (hazard ratio (HR) 0.85; 95% confidence interval (CI) 0.75–0.97;  $p = 0.02$ ).<sup>15</sup> The results of these studies provide a basis for discussing the potential benefits of radiation therapy in older adults.

Hormonal therapy is widely used in the adjuvant treatment of breast cancer because the proportion of hormone-receptor-positive tumors increases with age. This is illustrated in a study of the San Antonio and SEER databases. In patients between the ages of 55 and 64, roughly 83% of tumor specimens were estrogen-receptor positive compared with 90% between the ages of 75 and 84.<sup>16</sup> In addition, data from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of clinical trials demonstrate that hormonal therapy has similar efficacy in younger and older adults.<sup>17,18</sup>

The available options for hormonal treatment include tamoxifen or an aromatase inhibitor. Several studies demonstrate a benefit with an aromatase inhibitor in improving disease-free survival when given upfront or in sequence after tamoxifen.<sup>19-24</sup> However, several questions remain regarding the optimal duration of hormonal therapy as well as the best way to integrate tamoxifen and an aromatase inhibitor.<sup>25</sup>

There are conflicting data regarding the efficacy of adjuvant chemotherapy with increasing age. Data from the EBCTCG demonstrate

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a decreasing benefit from adjuvant chemotherapy with increasing age.<sup>17</sup> On the other hand, an analysis of data from four CALGB clinical trials demonstrated that older patients derived benefits similar to younger patients from the treatment arms that contained 'more' versus 'less' chemotherapy.<sup>11</sup> However, older patients were at increased risk for treatment-related mortality. In contrast, a review of the SEER Medicare database, including 35,060 women aged 65 or older with all stages of breast cancer, demonstrated no association of advanced age with the rate of hospitalization or death from toxicity related to chemotherapy.<sup>26</sup>

These results parallel several other studies that show no relationship between age and chemotherapy-related toxicity.<sup>27,28</sup> A limitation of these studies is that they likely included a select group of older patients who were chosen to receive the therapy.

Older patients are less likely to receive adjuvant chemotherapy than younger patients. An evaluation of the MD Anderson database demonstrated that 83% of patients between the ages of 55 and 64 received adjuvant chemotherapy compared with 29% above the age of 70.<sup>29</sup> This age-related decline in treatment with adjuvant chemotherapy is demonstrated even among women with hormone-receptor-negative breast cancer where chemotherapy is the only option that decreases the risk of relapse and mortality.<sup>30</sup>

The factors influencing the recommendation for adjuvant chemotherapy in patients with high-risk breast cancer were explored in a survey of oncologists at two academic institutions. When asked whether adjuvant chemotherapy should be given in simulated patients of varying age and health status, patient age influenced the decision-making process in 96% of physicians. Even after controlling for health status, a significant difference emerged among groups stratified by age. For instance, all physicians surveyed opted to give adjuvant chemotherapy to a 70-year-old female patient in perfect health, whereas only 61% chose to do so in an 85-year-old female in similar health.<sup>31</sup>

In considering specific chemotherapeutic agents, anthracyclines represent a significant component of most adjuvant regimens for breast cancer. However, with increasing age there is a decreasing tendency to prescribe anthracyclines. In the aforementioned survey of oncologists at two academic oncology centers, nearly all respondents

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opted to administer an anthracycline-containing regimen to a simulated 70-year-old patient with node-positive, hormone-receptor-negative

breast cancer. However, in an 85-year-old female with otherwise similar characteristics, the decision to apply anthracycline-based therapy fell to approximately 20%, with a near equal tendency to give either non-anthracycline therapy or no chemotherapy at all in the remainder of the respondents.<sup>31</sup>

Concerns regarding toxicity may cause this hesitancy to prescribe anthracyclines. However, in a pharmacokinetic study of doxorubicin and cyclophosphamide administered to patients between the ages of 35 and 79, there was no significant age-related difference in clearance or toxicity.<sup>32</sup> Among practitioners, there may be specific concerns

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regarding cardiac toxicity related to anthracyclines, especially given the concomitant rise in cardiac comorbidities with age. In a cohort of 630 patients receiving doxorubicin and placebo through phase III trials, it was determined that patients 65 and older experienced a greater incidence of congestive heart failure compared with younger patients.<sup>33</sup> This finding was further supported by a recent review of the SEER-Medicare database. In this observational study of 34,621 female breast cancer patients between the ages of 66 and 90, anthracycline chemotherapy led to a significantly higher incidence of congestive heart failure compared with patients who received other types of chemotherapy (HR 1.45; 95% CI 1.19–1.76).<sup>34</sup> For patients with HER-2/neu-positive tumors, adjuvant trastuzumab is used to decrease the risk of relapse.<sup>35,36</sup> Although there are limited data in older adults, increasing age is a risk factor for trastuzumab-associated cardiomyopathy.<sup>37</sup>

Taxanes also represent a cornerstone of adjuvant breast cancer chemotherapy, and several studies have described variability in the pharmacokinetic profiles of older populations. In the largest of these trials, the CALGB assessed 122 patients divided into three separate cohorts stratified by age. These patients received paclitaxel at 175mg/m<sup>2</sup> over three hours every three weeks. Increasing age was associated with an increased area under the curve (AUC) and decreased mean paclitaxel clearance. With respect to toxicity, there was a lower absolute neutrophil count nadir and a greater incidence of grade 3–4 neutropenia, although this did not result in more episodes of fever, hospitalization, or antibiotic administration.<sup>38</sup>

Current studies are exploring alternative chemotherapeutic regimens in older adults. The Intergroup recently completed a trial comparing adjuvant adriamycin and cyclophosphamide or cyclophosphamide, methotrexate and fluorouracil versus capecitabine for the adjuvant treatment of breast cancer in older adults. The efficacy data are

still pending. Although an oral chemotherapeutic regimen is appealing in an older adult, the potential for toxicity is still present. In particular, for patients receiving capecitabine, careful attention to dosing based

the patient's medication regimen should be scrutinized, such as the use of folate supplementation. One study correlated increased mean serum and red blood cell folate levels with capecitabine-related toxicity.<sup>40</sup>

## Older patients were at increased risk for treatment-related mortality.

on renal function is needed. In addition, there is potential for drug–drug interactions. For instance, capecitabine exacerbates the anticoagulant activity of warfarin, and should prompt cautious and more frequent monitoring.<sup>39</sup> Even seemingly benign components in

## Future Directions

Throughout this discussion, it becomes evident that most of the data available for older adults are derived from retrospective studies. Assessing therapeutic modalities in prospective clinical trials that include older adults would provide valuable information in a more timely fashion within this demographic. Inclusion of a geriatric assessment in clinical trials may also help to identify factors other than chronological age (such as functional status or comorbid medical conditions) that help to predict which older patients are at risk for therapy-associated complications and thus lead to interventions that decrease this risk while administering therapy.<sup>41</sup> Data from such prospective trials are needed in order to establish evidence-based guidelines for management of older patients with cancer in general, and breast cancer in particular, a population that is projected to grow by an astounding 72% by 2025.<sup>42</sup> ■

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