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## Role of Adjuvant Therapy in Older People with Breast Cancer

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### ABSTRACT

The expanding population of older people with breast cancer is challenging for the clinician. While a wealth of data on younger women assists doctors in the discussion of adjuvant therapeutic options, these are not necessarily applicable to older women. This issue is discussed in this article in relation to the efficacy and toxicity of adjuvant chemotherapy, hormone therapy and biological therapy in the older population. The differing stage and biology of breast cancer in the elderly is also highlighted. The development of using the Comprehensive Geriatric Assessment tool in the clinical assessment of older patients is also outlined.

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### INTRODUCTION

It is estimated that 1 in 11 women will be diagnosed with breast cancer and in women aged 80 years the risk increases to 1 in 8. Geriatric oncology, a burgeoning subspecialty of oncology, has developed as a discipline through recognition of the rise in age of the cancer patient and the issues of prognosis and toxicity that are peculiar to this cohort. This article is a discussion on the literature pertaining to the systemic management of early breast cancer in the older population. The literature defines the older patient with breast cancer variously as being 65 years or older and 70 years or older.

Adjuvant therapy is intended to sterilise micrometastatic disease through the use of systemic therapy after the initial surgical resection of the primary cancer. The rationale for this as an approach to cure or improve disease-free survival and overall survival is based on Level I and II evidence.<sup>1</sup>

All age groups and sexes derive benefit from adjuvant therapy, but the absolute benefit derived depends on prognostic and predictive factors. In relation to prognostic factors, the greater the chance of relapse, the greater the absolute benefit derived from treatment. To assess prognosis, oncologists use tools such as Adjuvant!.<sup>2</sup> Disease-related data such as tumour size, nodal status, tumour grade, and hormone receptor status are incorporated in the assessment of the risk of relapse. A high tumour grade and lack of hormone receptor expression reflect a less differentiated, more aggressive cancer.

Nevertheless, prognostic factors do not take into account the impact of adjuvant therapy. Predictive factors, however, measure the probability of benefit from treatment; the higher the oestrogen receptor expression, the greater the response to hormone therapy. Conversely, the lack of oestrogen

receptor predicts a greater likelihood of response to chemotherapy. Not surprisingly, evidence of human epidermal growth factor (HER2) receptor over-expression predicts a greater likelihood of efficacy with the use of biological therapy.

### EPIDEMIOLOGY AND PROGNOSIS

There has been a rise in the incidence of breast cancer, partly explained by the impact of mass screening programs. This will be more noticeable in the older population, which continues to grow as life expectancy improves, particularly in the Western world.

A number of confounding factors require consideration when assessing the prognosis of older women. Staging tends to be less meticulous in the older patient, for example, evidence of less axillary staging undertaken in the 70 years or older group, and more so, in those aged 80 years or older.<sup>3</sup> Axillary staging is regarded as routine practice in younger patients but data from the Netherlands indicate that clinicians were reluctant to stage older patients. In 1997, 23% of patients aged 70 to 80 years did not undergo axillary staging, and this rose to 42% in patients aged over 80 years. This was presumably due to concerns regarding the morbidity of the procedure and a sense that the prognostic information derived from staging ultimately impacted less on subsequent adjuvant treatment decisions.

With the advent of sentinel node biopsies, the morbidity of axillary staging has lessened substantially. This has resulted in an increase in axillary staging in the Netherlands. The follow-up data in 2005 suggested that axillary staging with sentinel node biopsy had led to a decrease in unstaged women aged 70 to 80 years (13%), but no change in practice was apparent in women aged over 80 years.

In a recent review, the proportion of patients with advanced disease (Stage III/IV) was higher among older patients compared to younger women. Despite this, breast cancer in many elderly women takes on a relatively indolent time course. This is supported by Italian data suggesting the 'elderly' phenotype was usually one of low proliferation rates, higher oestrogen receptor content, lower HER2 expression rates, and lower p53 accumulation.<sup>4</sup> It should be noted that 20 to 30% of older women present with a more aggressive picture, with a higher-grade tumour and negative hormone receptor expression.

It is difficult to ascertain whether prognosis in older patients is better or worse without incorporating the impact of adjuvant therapy. Older patients are less often offered modalities such as adjuvant radiotherapy or chemotherapy. Although this is commonly justified on the basis of chronic illness or comorbidity, this is not always the case. In a study of radiotherapy use, old age was a strong factor for not receiving adjuvant radiotherapy than comorbidities. Thus, age is sometimes confused with frailty.

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## ADJUVANT THERAPY

Despite the overall benefits of adjuvant therapy, the applicability of the data from adjuvant trials to the older population is questionable. The proportion of patients aged 65 years or older in three Cancer and Leukemia Group B studies was 9%, and 3% were 70 years or older.<sup>5</sup> It was likely that recruitment was biased in favour of fitter patients, as the third generation regimens are considered to be more toxic.

Data would suggest that older patients are commonly not offered what would be regarded as standard treatment in women under 70 years of age. The reasons for this are multiple—from the physician standpoint, this may reflect concerns with increased risk of toxicity and the greater number of comorbidities in the elderly. This may also reflect a degree of ‘ageism’ and an underestimation of the life expectancy of patients.<sup>2,6</sup> In reality, patients aged 70 years or older and in perfect health can expect to have an average additional life expectancy of 16 years, and a 75-year-old woman, 12 years.

Patients can be nihilistic when considering adjuvant therapy. Evidence suggests that older patients have a resigned approach to illness, commonly experience denial related to cancer diagnosis, or have misconceptions on cancer and treatment benefits.

To better quantify a patient’s probability of benefiting from adjuvant therapy, a tool created by Peter Ravdin (known as Adjuvant!) uses the Surveillance, Epidemiology, and End-Results registry data to estimate 10-year disease-free survival and overall survival with and without adjuvant chemotherapy and hormone therapy.<sup>2</sup> This tool is very useful in older patients, using an estimate of comorbidities to assess also the risk of death from other causes. This assists the clinician in making an objective assessment of benefit, thus providing patients with clear information and choice. Having said this, the tool is derived from 1998 overviews of randomised trials, and the number of older patients represented in these trials was small.

## Chemotherapy

### *Efficacy*

The Early Breast Cancer Trialists’ Collaborative Group data demonstrated that the subset of postmenopausal women with oestrogen receptor positive disease derive a small benefit from chemotherapy.<sup>1</sup> In these studies, only 4.3% of patients were older than 70 years (1224 out of a total of 28 764 women). There are few studies examining the question of treating the elderly with adjuvant chemotherapy. The French Adjuvant Study Group 01 trial specifically set out to examine this question and randomised patients 70 years or older to tamoxifen with or without low-dose weekly epirubicin.<sup>7</sup> The study confirmed a small but definite advantage with the addition of epirubicin.<sup>7</sup>

The question of oestrogen receptor negative disease in postmenopausal women has not been examined in a dedicated randomised study. The Early Breast Cancer Trialists’ Collaborative Group data, however, are clear that, unlike patients with oestrogen receptor positive disease, the benefits from chemotherapy in oestrogen receptor negative disease is substantial and consistent across all age groups.<sup>1</sup> A report from the Memorial Sloan-Kettering Cancer Center showed less chemotherapy use in the elderly compared with younger patients, but elderly patients who did receive treatment benefited from a 15% reduction in all-cause mortality.<sup>8</sup>

The future of research in geriatric oncology needs to tailor approaches to the needs of older patients. One such approach from the International Breast Cancer Study Group aims to devise an adjuvant chemotherapy regimen suitable for the older patient. In one study, liposomal doxorubicin is being compared to

observation, and in another, compared with low-dose (metronomic) cyclophosphamide and methotrexate.

### *Toxicity*

The challenge to deliver evidence-based chemotherapy at an effective dose in the elderly is the risk of infection. Haematological toxicity is more apparent in older patients.<sup>5</sup> In the Muss analysis of the Cancer and Leukemia Group B studies, patients aged 65 years or older were 66% more likely to have Grade 4 leucopenia than women aged 50 years or younger, and were twice as likely to be admitted for febrile neutropenia. This study also suggested that the incidence of Grade 3 to 4 non-haematological toxicity (e.g. stomatitis, diarrhoea, peripheral neuropathy) in older women was no greater than in younger women.

Two rare toxicities in the form of heart failure and acute myelogenous leukaemia may be more likely following adjuvant chemotherapy in women aged 65 years or older. Patt et al. evaluated 64 517 women over the age of 65 years with Stage I to III breast cancer for the incidence of acute myelogenous leukaemia.<sup>9</sup> Women who had received adjuvant chemotherapy had an absolute risk of acute myelogenous leukaemia of 1.8%, compared with 1.2% in women who had not received chemotherapy. An extreme age of over 80 years was associated with a higher risk (HR 3.35) compared with women aged 66 to 70 years. There was no chemotherapeutic drug or regimen that conferred a lower risk, with cyclophosphamide and anthracyclines appearing equivalent in risk, and the addition of taxanes having no impact. Previous studies assessing acute myelogenous leukaemia quoted risks of 0.55% over eight years with epirubicin-cyclophosphamide-based regimens (this study included mainly young women, often under 50 years of age).<sup>10</sup>

A similar review of the Surveillance, Epidemiology, and End-Results registry data collected information from 43 338 women aged 66 to 80 years with Stage I to III breast cancer, and assessed the impact of adjuvant chemotherapy on cardiac function.<sup>11</sup> The group was divided into three cohorts: those who did not receive chemotherapy; those who received anthracycline-based chemotherapy, and those who received non-anthracycline-based chemotherapy. The cohorts that received chemotherapy were slightly younger and healthier. People with chronic medical conditions were under-represented in the anthracycline group. Analyses were divided into age groups of 66 to 70 years, and 71 to 80 years. Curiously, women aged 66 to 70 years were at a greater risk of anthracycline-induced cardiotoxicity, despite their better condition. At 10 years follow-up, 38.4% of the anthracycline group in the younger age bracket had developed congestive heart failure, compared with 32.5% for non-anthracycline-treated patients, and 29% for the no chemotherapy group. Although women aged 71 to 80 years had a greater cumulative risk of congestive heart failure compared to their younger counterparts, the rate of congestive heart failure was not greater in the chemotherapy-treated groups. Multivariate analysis confirmed that women aged 66 to 70 years had a 26% greater risk of congestive heart failure than women receiving non-anthracycline regimens. Other independent risk factors included age, vascular disease, diabetes mellitus, emphysema and trastuzumab use.

It is worth noting that in the follow-up period, 37.8% of deaths were attributed to breast cancer and only 1.3% to congestive heart failure (as the primary cause). As always, the decision on adjuvant chemotherapy and the use of anthracyclines needs to be taken in the context of the risk of breast cancer death, the absolute survival gain resulting from chemotherapy, and the comorbidities of the individual patient.

The mechanism for increased toxicity in the elderly, partly relates to comorbidity but also to the differing pharmacokinetics in this population. It is well known that hepatic and renal clearance is reduced in older people. Unfortunately, there is a dearth of data assessing the pharmacokinetics of chemotherapy in the elderly.<sup>12,13</sup> Most clinicians make a judgement on the dose for an individual patient, and empirical dose reductions for the first cycle are likely to be a common practice.<sup>14,15</sup>

## Hormone Therapy

### Efficacy

In contrast to adjuvant chemotherapy, adjuvant hormone therapy has been examined in more detail in the elderly. Again, the median age of postmenopausal patients in adjuvant hormone therapy trials was lower than the age regarded as 'elderly'.<sup>16</sup> Nevertheless, the toxicities of hormone therapy are not regarded as more frequent or severe in the elderly.

The initial studies of adjuvant hormone therapy have demonstrated the advantage of tamoxifen and this was confirmed in the Oxford Breast Cancer Overview.<sup>17</sup> Recently, aromatase inhibitors have been examined in the metastatic and early setting. Through inhibition of aromatase that converts testosterone and dehydroepiandrosterone to oestrone and oestradiol, the latter levels drop by 91 to 93% in patients treated with aromatase inhibitors. Three types of randomised studies have examined the role of aromatase inhibitors as adjuvant therapy. Two studies have demonstrated that upfront aromatase inhibitors for five years are superior to five years of tamoxifen, with improved disease-free survival. Further studies have shown that patients treated with two to three years of tamoxifen have improved disease-free and overall survival when switched to an aromatase inhibitor versus continuing with tamoxifen.<sup>18</sup> It is reasonable to conclude that this advantage is maintained in the elderly group. The recent consensus statement supported the notion that postmenopausal women should receive an aromatase inhibitor at some point in the course of their treatment.<sup>19</sup>

The issue of hormone therapy in older patients has become more pertinent with the data from the Canadian study MA. 17.<sup>16</sup> It should be noted that the treatment of oestrogen receptor positive early breast cancer through control of micrometastases might require a long-term strategy. In oestrogen receptor positive early breast cancer, 50% of relapses occur after the five-year mark, when women traditionally cease tamoxifen. Interest in providing chronic hormone therapy waned following the negative results of the National Surgical Adjuvant Breast and Bowel Project Study B-14, which showed no advantage for ten years of tamoxifen over five years.<sup>20</sup> The MA. 17 study has since demonstrated that five years of letrozole following five years of tamoxifen leads to significant improvements in local recurrence and distant-disease-free survival.<sup>16</sup> Furthermore, the hazard ratios for relapse continue to fall as treatment with letrozole continues over the five years, supporting the notion that duration of treatment is important for ongoing benefit.<sup>21</sup> A further randomisation of patients after five years of letrozole to further treatment or placebo will contribute to our understanding of the need for chronic or possibly lifelong treatment of oestrogen receptor positive disease.

### Toxicity

The toxicities of hormone therapy are well known and the differing side effects of tamoxifen and aromatase inhibitors are important to consider in decisions regarding adjuvant therapy. Tamoxifen can rarely cause uterine cancer, thrombosis

and cerebrovascular events, whereas aromatase inhibitors result in osteopenia. What is unclear from the literature is whether older patients are more susceptible to these toxicities. Certainly, the morbidity and mortality of hip fractures in older women is well documented.

The decision as to whether a patient receives tamoxifen or an aromatase inhibitor or a sequence of the two requires consideration of their toxicities. Ongoing therapy often demands a management of common troublesome toxicities such as hot flashes, vaginal dryness or discharge, arthralgia, and psychosexual and cognitive dysfunction.

The bone demineralisation effects of aromatase inhibitors are a concern in a population that typically has sustained bone loss since menopause. In comparison to tamoxifen, which has a protective effect on bone density, the aromatase inhibitors in several randomised studies have demonstrated an excess fracture risk (2 to 3%). Interestingly, the 68-month follow-up of the Arimidex, Tamoxifen, Alone or in Combination study showed an equivalent fracture rate following anastrozole cessation at five years, in comparison to the tamoxifen arm.<sup>22</sup>

Oncologists are increasingly aware of the need to monitor the bone health of their breast cancer patients. The use of aromatase inhibitors has led to an increase in bone mineral density assessments, and measures of bone turnover, such as N-telopeptide X. Recommendations for the introduction of exercise, vitamin D, calcium supplements and bisphosphonates are now well established.<sup>23,24</sup>

## Biological Therapy

There is tremendous interest in targeted therapies for breast cancer. Targets such as the *erb* family of receptors, or vascular endothelial growth factor receptor are attractive for drugs such as monoclonal antibodies and small molecule tyrosine kinase inhibitors. The therapy that is now standard of care in breast cancer is trastuzumab, a humanised monoclonal antibody directed against the HER2 (or c-erbB2) receptor. Trastuzumab has proven to prolong the disease-free and overall survival of women with early and advanced breast cancer that over-expresses HER2 protein, as proven by immunohistochemistry or fluorescence *in situ* hybridisation analysis (assessing presence of HER2 gene amplification).<sup>25,26</sup>

What is less clear is the applicability of the adjuvant biological therapy to the elderly. It would be fair to presume that trastuzumab's benefit is similar in patients aged 65 years or older. It should be noted that the number of patients older than 60 years in the B-31, N9831 and HERA adjuvant studies was only 15%, so it is difficult to draw conclusions from these data.<sup>25,26</sup>

What is clear is that the concerns of cardiac toxicity associated with the use of trastuzumab are greater in older patients. Romond's analysis of the cardiac safety data from the National Surgical Adjuvant Breast and Bowel Project Study B-31 showed, that patients older than 50 years with a multiple gated acquisition scan of 50 to 54% post-anthracycline therapy had a three year cumulative incidence of congestive heart failure of 20% with trastuzumab therapy.<sup>27</sup>

The data from the Breast Cancer International Research Group 006 study may assist in directing the clinician towards a less toxic regimen.<sup>28</sup> It supports the efficacy of a non-anthracycline based regimen (trastuzumab-carboplatin-docetaxel) that has a much lower incidence of cardiotoxicity compared with the anthracycline regimen (doxorubicin-cyclophosphamide followed by docetaxel-trastuzumab). The mature analysis of this study is awaited to draw firm conclusions.

## ASSESSMENT

The challenge is to assess the older woman for comorbidities that might either preclude the use of adjuvant therapy, or necessitate a dose reduction. Following this, the use of Adjuvant-On-Line can aid clinicians and patients in the process of making an informed choice regarding treatment.<sup>2</sup>

The traditional oncological tool of the performance status assessment is rudimentary in the face of the frailty and health issues of many older patients. A sophisticated tool devised by geriatricians is the Comprehensive Geriatric Assessment, which through a variety of assessments (cognitive, functional, biochemical) can either help identify frail patients who should avoid treatments with toxicity, or optimise their condition to enable them to manage their treatment more successfully. Despite its promise, the Comprehensive Geriatric Assessment tool has been used sparingly by the oncology community.

The discussion of principles of adjuvant therapy is at best, complex and time consuming. It is important to understand that the information needs of older patients may differ from younger patients. An interesting study of older patients with advanced colorectal cancer suggested that 50% did not want detail on prognosis and preferred to be passive, and 25% wanted to leave all decisions to their physician.<sup>29</sup> In this and other studies, there was a clear discordance between the physician's assessment of the patient's preference for information and the patient's stated desire for information. One may conclude that the modern trend towards shared-decision making may not always be applicable to older patients.

## CONCLUSION

Older patients commonly have a set of health issues that require meticulous assessment, with the incorporation of the comorbidity management into the 'usual' treatment algorithms. Rather than developing age (and possibly 'age-ist') based protocols that may deny older patients effective therapy, it behoves clinicians to provide individualised and optimal care. For the researcher, a change in the paradigm of protocol design needs to incorporate questions that will result in practical, effective treatments for the older patient.

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