

Treating elderly patients with breast cancer

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Abstract With an aging population, the management of elderly patients with breast cancer is recognised as an area of increasing concern. This population, however, represents a heterogeneous group whom, on the basis of age alone should not be denied any appropriate interventions in the management of their breast cancer. This article reviews the current issues in treating these patients and the paucity of evidence in this setting.

Keywords: Breast cancer; Elderly; Treatment

Introduction

The management of elderly women with breast cancer is becoming an increasing issue due to the diverse state of their general health and the relative lack of evidence for treatment effect within this setting. Breast cancer incidence increases with age and currently 48% of breast cancer cases occur in women of 65 years and above, with over 30% occurring in those over 70 years [1]. The aging population is increasing and with the average life expectancy for a women aged 75 years being currently 11.1 years in Western Europe [2], the lack of evidence-based guidelines for them needs to be addressed. Aging is multifactorial and is associated with a decline in the functional reserve of multiple organ systems, as well as personal and social resources [1,3]. A difficulty in this setting is that there is no accepted definition of 'elderly'. Clinical trials often adopt arbitrary upper age limits, and trials designed for the elderly often start at 65 years with little representation in those over 75 or 85 years [2]. The older population with breast cancer need to be recognised as a heterogeneous group of patients whose biological, not chronological, age should be used to guide treatment

issues with recognition of their associated issues of increasing co-morbidities and often polypharmacy.

Recent data has shown the biological profile of breast cancer in the older population to be relatively favourable when a biological characterisation of 14 000 breast cancers showed a relation between advanced age and favourable biological characteristics including positivity for oestrogen/progesterone receptors, low proliferative rate, absence of p53 accumulation, bcl-2 overexpression and diploid DNA content [4].

However, despite this, elderly cancer patients still have a large breast-cancer-specific survival disadvantage [5] and in addition there is still a subset of older patients presenting with more aggressive disease (nodal involvement, large tumour size, HER-2 receptor overexpression and oestrogen-receptor negativity).

Primary treatment

Elderly patients presenting with breast cancer should receive the same assessment at presentation as younger patients. Age itself should not be seen as a barrier to surgical intervention as the main factor influencing surgical morbidity and mortality is not age but any pre-existing co-morbidities. Improvements in anaesthetics should allow most patients to undergo an appropriate procedure [6]. Primary medical therapy as a sole treatment should be reserved for those who are deemed by the multidisciplinary team as medically

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unfit for any other intervention as the analysis from Italian and UK data showed that breast-cancer-specific survival is worse in women treated with tamoxifen alone [7]. Those unfit patients will also benefit from the emerging data on aromatase inhibitors as primary therapy, illustrated by Ellis *et al.* with the improved response to letrozole over tamoxifen as neoadjuvant therapy [8].

Adjuvant treatment

The Oxford Overview confirmed the benefit of 5 years adjuvant tamoxifen in older patients with respect to recurrence and mortality for node-negative and node-positive oestrogen receptor positive disease and this remains the current standard [9]. The emerging data on aromatase inhibitors from the Arimidex, Tamoxifen, Alone or in Combination (ATAC) study shows anastrozole is associated with an improved disease-free survival over tamoxifen, however while anastrozole was associated with less endometrial cancer, there were more skeletal events which will have to be considered in this population with a potential increased risk of osteoporosis [10]. Recent data also shows a possible role for aromatase inhibitors in patients with overexpression of the HER-2 receptor as tamoxifen may be less effective in this setting [11,12]. It is important that any changes to adjuvant hormone strategies encompass the older population also.

The role of adjuvant chemotherapy in the older population is more controversial. The overview illustrated that polychemotherapy-influenced recurrence and survival in patients up to 69 years, although with decreasing benefit as age increased, but concluded that there are too few women over the age of 70 years studied to allow direct assessment of the effects of treatment among them [13]. There is more consensus on whom not to treat rather than those whose benefit of adjuvant chemotherapy outweigh the risks. Crivellari *et al.* felt the 'frail elderly' should not receive any form of adjuvant chemotherapy defined by one of the following conditions: age ≥ 85 years, ≥ 1 activities of daily living (ADL) dependence or presence of one geriatric syndrome, for example dementia, incontinence or falls [14]. Unfortunately, there is a lack of a standardised method of assessment in this population to help identify those most likely to benefit from adjuvant treatment, as the Karnofsky index/ECOG performance status scales are not sufficiently specific. Assessment tools are in use including the ADL scale, a co-morbidity scale and the mini-mental state evaluation but these are often not a part of routine practice [15]. A comprehensive geriatric assessment (CGA) is necessary which covers functional status, co-morbidity, mental status, emotional conditions,

nutritional status, polypharmacy and the presence of any geriatric syndromes, for example delirium, dementia, incontinence and neglect [1]. This would allow a better-informed decision to be made which encompasses the many facets of aging and the possible effects of adjuvant chemotherapy. A recent assessment of practice within the Breast International Group showed that biological age and biological characteristics of the tumour were the most frequently used criteria to propose adjuvant chemotherapy to an elderly patient [15].

It was also noted that only a minority of oncologists perform a geriatric assessment, however the majority of the participants in the survey were convinced about the need to use/validate a CGA as a predictive instrument of toxicity and/or activity of anticancer therapy in the elderly.

Pharmacology

The diversity of the elderly patient population in respect to age-related multisystem physiological changes has an effect on several aspects of pharmacology that need to be considered when tailoring chemotherapy regimens to minimise toxicity [16].

Aging influences all major pharmacokinetic parameters, absorption, distribution, metabolism and excretion. Currently most chemotherapeutic agents are administered intravenously but with novel emerging oral agents (e.g. capecitabine) and oral preparations of current intravenous agents (e.g. taxanes), this may become an increasingly relevant issue. The absorption of oral drugs may be affected by the reduced restriction in the absorptive surface of the small bowel and splanchnic circulation as well as changes in gastric secretions and decreased gastric motility [17]. Whereas these factors are important, the bioavailability of drugs does not seem to be affected at least up to the age of 80 years [18]. The associated alterations in body composition with aging are a decrease in total body water, increase in body fat and reduction in serum albumin [16]. These changes in body composition affect the volume of distribution (V_d), which is contracted for water-soluble drugs and expanded for fat-soluble drugs. Therefore, water-soluble drugs may have higher peak plasma levels with shorter half-lives and the reverse for lipid-soluble drugs. This may result in higher peak dose levels of drugs (e.g. anthracyclines) with possible potentiation of their toxicities within the elderly [16].

Changes affecting drug metabolism within the liver appear to be more related to polypharmacy and its potential interactions with the cytochrome p450 system [16]. The excretion of most chemotherapeutic agents is via the biliary or renal routes. There is an age-related decline in glomerular filtration rate that

needs to be accounted for to avoid excessive toxicity. The creatinine clearance can be calculated with formulae such as Cockcroft–Gault which accounts for age and weight; however serum creatinine alone is not always helpful due to possible overestimation of renal function as less creatinine is produced with a reduced lean body mass associated with increased age. Other formulae are available for adjusting the initial dose of chemotherapy (e.g. Kintzel and Dorr [19]).

While retrospective studies of clinical trials failed to demonstrate a relationship between age- and chemotherapy-related toxicity [16], caution is needed as the older population eligible for trials are unlikely to be representative of the true elderly population. There is evidence that age is an independent risk factor for toxicity (e.g. mucositis with fluorinated pyrimidines) [20]. The normal tissues whose susceptibility to chemotherapy increases with age include the mucosal surfaces, the heart, bone marrow, peripheral and central nervous system [21]. Myelotoxicity is more common in the elderly population; Dees *et al.* showed with adjuvant doxorubicin and cyclophosphamide the risk, duration and seriousness of neutropaenia increased with age and was particularly seen in those over 75 years [22]. Growth factors and prophylactic antibiotics with quinolones can help ameliorate this effect and should be considered for use in this susceptible population prior to dose reduction [23]. It is therefore important that elderly patients undergo an adequate assessment prior to chemotherapy and that regimens are tailored where possible to reduce therapeutic complications of cytotoxic treatment in this setting.

Metastatic disease

Endocrine therapy remains the initial treatment of choice for older patients with metastatic disease due to the low-toxicity profile and is used even up to third line in patients with hormone-receptor-positive disease. Aromatase inhibitors have shown superiority over tamoxifen in the metastatic setting and their use is increasing [24,25]. Trastuzumab is also helpful in the elderly due to its favourable toxicity profile in those with overexpression of the HER-2 receptor. Chemotherapy should be considered for hormone-receptor negative and those with aggressive disease but should be balanced with associated comorbidities of the patient. Newer drugs are being developed which are attractive in the elderly population, for example capecitabine allowing oral administration and reduced hospital visits, which can have a positive impact on quality of life. Alternative scheduling is attractive in this age group such as weekly taxanes being used in phase 2 trials with similar efficacy and less toxicity in the elderly patient [26]. The weekly regimens appear

to be associated with differing toxicity profiles to 3 weekly with more fatigue and fluid retention (docetaxel), peripheral neuropathy (paclitaxel) but less myelosuppression. Combination regimens tend not to be used in the elderly population as although a study of docetaxel and capecitabine showed a survival advantage [27]; in general combinations do not show a survival advantage and the increased toxicity makes them less attractive over sequential therapy in the elderly. Therefore chemotherapy is appropriate in this setting but a tailored regimen may help significantly reduce toxicity without compromising response.

Clinical trials

There continues to be a controversy on the management of elderly women with breast cancer due to the paucity of evidence from clinical trials in this population. This is concerning as although breast-cancer-specific mortality rates have declined among women less than 70 years, this is not the case for those over 70 years where they are either stable (70–79 years) or have increased (≥ 80 years) [28]. Hutchins *et al.* reported that in 16 936 patients enrolled in SWOG trials, patients ≥ 65 years formed 25% of enrollees despite forming 63% of the US population with cancer. It was more obvious in breast cancer where the elderly make up 49% of patients but only 9% of enrollees [29]. A recent article identified physicians as a key barrier to enrolment of older women in breast cancer clinical trials [30].

This issue is being addressed as the National Institute of Health has issued two grants: one to CALG B to study adjuvant chemotherapy in women with breast cancer over 65 years and the other to SWOG looking at treatment in those over 70 years with metastatic breast, bladder and colorectal cancer. However more trials are needed to be able to practice evidence-based medicine in this heterogeneous population to allow individualisation of treatment for the elderly.

Conclusion

The management of elderly patients with breast cancer is an area of increasing concern. These patients should not be denied interventions due to perceived intolerance but be assessed appropriately and considered for active treatment both in the adjuvant and metastatic setting. It is accepted that tailoring of regimens may be necessary to avoid excessive toxicity but prophylactic measures should also be considered to prevent reversible complications of treatment and maintain quality of life. The needs of the elderly should not be ignored, with our aging population the oncologist should recognise this diverse group whose

specific problems need to be addressed by prospective clinical research.

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