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Management of breast cancer in older and frail patients

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ABSTRACT

Almost 50% of breast cancer occurs in women over the age of 65 years. The incidence of non standard adjuvant treatment increases with age and this group are under represented in clinical trials. We discuss tools to aid patient selection and adjuvant treatments including surgery, radiotherapy and systemic therapies for this group of patients.

Introduction

The incidence of breast cancer rises with age and almost 50% occur in women over the age of 65. There is good evidence that older patients are less likely to have standard therapies [1–4] or be more likely to discontinue standard treatments [5]. There are many possible reasons for this, some of them entirely valid. Nevertheless the consistency of these data raise concerns that treatment of elderly or frail patients with early breast cancer may frequently be sub-optimal.

Are older patients being managed appropriately?

There are several studies suggesting that non-standard management of early breast cancer increases with age. In a UK population based cohort study involving casenote review of 480 women aged 65 years or more, 19% failed to have triple assessment (N = 305), 22% did not have surgery (N = 305), 17% did not have axillary node surgery (N = 236), 41% did not have radiotherapy following breast conserving surgery (N = 130) and 41% did not have oestrogen receptor (ER) testing (N = 412) [2]. Data from elsewhere including North America and Mainland Europe have likewise suggested that non-standard management increases with age even taking into account tumour characteristics [1,3,4].

It is of course plausible these differences in treatment reflect biological differences in breast cancer in the elderly requiring different therapies. To some extent this is true, but data comparing tumour characteristics with increasing age from 55 to >85 years suggest that there are only small differences in node negativity, S-phase fraction, ER positivity, and HER2 negativity [6].

There are of course other factors that might influence treatment selection in older women including psycho-social issues, differences in pharmacokinetics including drug absorption, hepatic metabolism, renal function, differences in pharmacodynamics including drug elimination, differences in normal tissue toxicity including impaired bone marrow reserve, impaired mucosal protection, impaired cardiac function, impaired neurological function, performance status and last but by no means least patient preference. Even taking these factors into account, the incidence of non-standard therapies is clearly of concern and raises 2 issues: first, it is important to ensure that elderly patients who are otherwise fit should receive standard treatment; second, the onus is on those of us involved in clinical breast cancer research to explore and identify effective therapies with minimal toxicity. It is entirely plausible that some elderly or frail patients may be prepared to trade a little in efficacy in exchange for markedly less toxic treatments. This concept will be addressed further, below.

Clinical trials involving elderly patients

It is clear from the literature that until recently elderly patients with breast cancer have usually been proportionately under represented in clinical trials. In a review of SWOG trials it was found that only 9% of elderly patients with breast cancer were entered

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into trials, despite 49% of all elderly cancer patients having breast cancer [7].

Likewise in the EBCTCG Oxford Overview of 60 trials involving 29,000 women comparing chemotherapy with none only 4% were 70 or older [8].

Recently trials specifically addressing older patients have begun to emerge and this trend must continue.

Surgery

As described above, a retrospective UK survey found that over 20% of patients over the age of 65 did not have surgery [2]. The importance of surgery was emphasized in a CRC UK trial involving 451 women aged 70 years or over who were randomized to tamoxifen alone versus surgery and tamoxifen. In the initial results with 34 months median follow-up there was a significantly higher local-regional relapse rate in patients who had tamoxifen alone (23% versus 8%) [9]. A subsequent late follow-up after a median of 15 years found that 40% of patients initially treated with tamoxifen alone eventually had to go undergo local surgery, and both overall mortality (HR1.29) and breast cancer mortality (HR1.68) were significantly worse [10].

A more recent Cochrane review has confirmed that surgery with or without tamoxifen is superior to tamoxifen alone in terms of overall mortality, progression, and local recurrence [11].

Radiotherapy

As described above, there is evidence that a significant proportion of elderly patients with early breast cancer do not receive radiotherapy after breast conserving surgery.

Although this is of concern, it may well be that for some older women this is appropriate. Older age is in itself a factor that predicts for a lower risk of local recurrence following breast cancer surgery [12].

Recently the PRIME (Post operative Radiotherapy In Minimum risk Elderly) trial randomized 1326 women aged 65 or over to whole breast radiotherapy and endocrine therapy versus endocrine therapy alone following breast conserving surgery. The entry criteria were tumour no larger than 3 cm, node negative, with a greater than 1 mm margin and ER-positive. After a median follow-up of 5 years, ipsilateral breast cancer recurrence was 1.3% (95% confidence interval 0.2–2.3) in women assigned to whole breast radiotherapy versus 4.1% (95% confidence interval 2.4–5.7) in those given endocrine therapy alone (p 0.002.) [13]. Predictably there was no significant difference in overall survival between the two arms.

In an earlier similar trial with longer follow-up, 636 women aged 70 or over with Stage 1 (T1N0M0), ER positive breast cancer were randomized to tamoxifen with or without radiotherapy following lumpectomy. After a median 5 years follow-up local recurrence was 1% for those treated with radiotherapy versus 4% for those given tamoxifen alone ($p < 0.001$) [14]. With 10 years median follow-up the respective local recurrence rates were 2% versus 9%, with no overall survival difference [24].

Although these differences are statistically significant, they are small in absolute terms and it may well be that many older patients with good prognosis breast cancers would be happy to forgo radiotherapy if given the choice, on the basis of only a very small increased risk of local recurrence. The resource savings would likewise be significant.

Endocrine therapy

In the BIG1-98 trial comparing adjuvant letrozole with tamoxifen for 5 years, an STEPP (subpopulation treatment effect pattern plot) analysis was used to look at the influence of age based on 3 groups: younger than 65 (N = 3127); 65–74 years (N = 1500); and 75 years or older (N = 295). Letrozole was significantly more effective than tamoxifen in terms of disease free survival in all age groups, despite the fact that elderly patients were less likely to complete trial treatment [15]. The incidence of bone fractures did not differ by age, although in all groups they were observed more frequently with letrozole than with tamoxifen. There were no significant differences between the two therapies for thromboembolic or cardiac adverse events. The study's conclusion was that age should not unduly affect the choice of adjuvant endocrine therapy.

Adjuvant chemotherapy

In the past, elderly patients were strikingly under-represented in adjuvant chemotherapy trials. In the Oxford Overview Analysis, 29,000 women were included in trials of chemotherapy versus none but only 1200 of these (4%) were aged 70 or older [8].

In the largest assessment of adjuvant chemotherapy in older women, 41,390 women aged 65 or over with Stage 1–3 disease were identified from the SEERS database. Of these, only 4500 (10.9%) were given adjuvant chemotherapy. The chances of receiving chemotherapy fell off markedly with age as follows: aged 65–69, 21%; aged 70–74, 13%; aged 75–79 8.6%; aged 80 or over only 2.4%. It was notable that survival benefit was seen only for patients who had both nodal involvement and ER negative disease. In the larger subset with ER positive disease, no benefit was seen, even for patients with nodal involvement [3].

More recently specific trials addressing adjuvant chemotherapy in older women have begun to emerge. CALGB49907 compared capecitabine with standard CMF or AC in 633 women aged 65 or older with early stage breast cancer. Capecitabine proved inferior both in terms of relapse free survival (3 years 85% v 68% $p < 0.01$) and overall survival (3 years 91% v 86% p0.02). This was disappointing since capecitabine was associated with a low incidence of serious toxicities [16]. It is to be noted however that in an exploratory subset analysis the benefit appeared mainly to be in patients with ER-negative cancers.

It is possible that we are overlooking potential benefits with other relatively low toxicity adjuvant chemotherapy for older women on the basis of very minor reductions in efficacy. For example, the CALGB40101 trial compared standard adjuvant AC with single agent paclitaxel and also 4 versus 6 cycles of chemotherapy, in a 2x2 design. 3871 patients were included with a median age of 53 years range (24–84 years). The initial analysis showed that for all treatments 4 courses were as effective as 6 [17]. In the comparison of weekly paclitaxel with standard adjuvant AC the conclusion was that “this trial did not show non-inferiority of paclitaxel to AC' and the trial was considered negative despite the further conclusion that ‘Paclitaxel was less toxic” [18]. However this conclusion was based on a 5 year relapse free survival difference of only 3% (91 v. 88%) and a 5 year overall survival difference of only 1% (95 v. 94%). It is entirely possible that elderly or frail patients might be very happy to opt for single agent paclitaxel with very much less toxicity, on the basis of such a small reduction in efficacy. There is an urgent need for further trials of less toxic versus standard chemotherapy schedules, based on the same premise.

Trastuzumab

The combined NSAPB-31/NCCTGN9831 US trials of standard chemotherapy with or without adjuvant trastuzumab for 1 year involved 16% patients over 60 years old and their benefit with trastuzumab was at least as good as for younger women (HR 0.51) [19]. Likewise in an exploratory sub-group analysis of the HERA