Early stage breast cancer in older adults

In: Geriatric Oncology, Martine Extermann (Ed.), Springer Nature

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Keywords: adjuvant, neoadjuvant, breast cancer, chemotherapy, endocrine therapy, radiotherapy, surgery, anti-HER2 therapy

ABSTRACT

Breast cancer is the most common cancer afflicting women worldwide. Its incidence peaks around 70 while mortality increases greatly after 75 yo. Given the competing risks on mortality with multimorbidities, geriatric assessment is a leitmotiv and is considered as the mandatory and non-opposable strategy to use for personalizing treatment. This is especially true for strategies used in early-stage breast cancer since benefits are expected to come with long follow-up.

Therefore treatment choice needs careful assessment of the benefit/risk balance and guidance according to a general health status assessment, in order to avoid jeopardizing functional status and quality of life.

This chapter will highlight the unmet clinical needs, future opportunities and adjusted strategies for local treatments (surgery and radiotherapy) and systemic treatments (chemotherapy, endocrine therapy and anti-HER2 treatment) in the older patients with early-stage breast cancer.

INTRODUCTION

Around 40% of breast cancers (BC) occur in women aged 65 and older and 20% in women over 75. Mortality increases greatly after 75 [Biganzoli 2012]. This contrasts sharply with the iconic and unfair portrayal of BC in the media and social attitudes.

Of note, co-morbidities increase in number and severity according to age [book chapter "comorbidity in aging and cancer" by Ramsdale et al]. They compete with BC prognosis and make necessary to prioritize medical problems and to individualize treatment referring to a geriatric assessment [book chapter "Comprehensive Geriatric Assessment (CGA) for Cancer Patients" Alexander]

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A further problem is that older BC patients in trials are fitter than the wider population of older patients, creating important gaps between approvals and applications in routine practice [book chapter "research methods" by Wildiers & Le Saux]. Indeed the lack of trial guidance for older BC patients has resulted in both over-treatment (given the higher risk of toxicities and competing causes of mortality) and under-treatment (because of age-based restrictions).

As for more advanced and/or metastatic cases [book chapter "systemic Treatment of Metastatic Breast Cancer in Older Adults" Mislang], management of early-stage BC in the older person requires specific adjustments and considerations for the different modalities available: surgery, radiotherapy and systemic treatments.

SURGERY

An ancient dictum says, ‘Good surgeons know how to operate, better ones when to operate, and the best when not to operate.’ Can we not operate or operate ‘less’ on BC in the older adults in relation to the primary tumour and the axilla? Differing tumour biology according to age, the use of systemic therapy, and mortality due to competing causes of death are the core issues to consider behind this question.

Surgery to the Breast

Over a century ago, George Beatson, a surgeon from Glasgow, first reported the use of endocrine manipulation (using a surgical approach at the time i.e. oophorectomy) in inducing a complete clinical response on a young woman with inoperable recurrent BC [Beatson]. A Cochrane review of seven small randomised controlled trials comparing surgery with primary endocrine therapy, primarily using tamoxifen for oestrogen receptor (ER) unselected tumours, in a total of 1,571 older adults, does not show any significant difference in overall survival (OS) [Hind]. A later systematic review of six of these trials and also 31 non-randomised studies demonstrates an advantage for surgery over primary endocrine therapy in terms of disease control and a likely survival benefit in older adults with a predicted life expectancy of five years or more [Morgan]. Patients treated only with aromatase inhibitors (AI) were found to have superior rates of disease control when compared to tamoxifen. Our group was involved in two of these randomised controlled trials and the long-term results show a significant correlation between the efficacy of primary endocrine therapy and ER status e.g. the 10-year local failure rate decreased from 80% to 43%

from the first trial (ER unselected) to the second one (ER H (histochemical) score ≥100 (out of a maximum of 300) required) [Chakrabarti, Johnston]. We have also analysed a consecutive cohort of 1,065 older women with ER (H-score ≥50) positive tumours treated by either surgery or primary endocrine therapy over a 37-year period in a single institution and noted no difference in BC specific survival rates between both groups when the H score was ≥250 [Syed 2011]. With tamoxifen being used in 69.3% of the patients receiving primary endocrine therapy, the median time to progression was 49 months (4 – 132 months), which was significantly prolonged with the use of an AI [Syed 2011]. All this data suggests that primary endocrine therapy may produce comparable survival outcome to that of surgery in patients with strongly ER+ tumours. Our work along a similar line shows that not just that BC in older adults tend to be ER+, they are more ER rich. In a series of over 3,000 primary BC patients, the peak H-score in all age groups was found to be between 100 – 200 with the exception of those ≥70 years, when it was between 200 – 300 [Cheung]. Partitional clustering of a panel of 24 biomarkers measured by immunohistochemistry (IHC) of tissue microarrays constructed from surgical specimens from our institution has also demonstrated differing biology according to age, with a unique subtype, 'low ER luminal', showing low ER expression and over-expression of luminal cytokeratins), identified in the older population [Syed 2013]. In summary, if we were to consider not operating on an old adult with BC, someone with an ER rich tumour (approaching an H-score of 300 or equivalent) may be the right person from the biological perspective, as long as systemic endocrine therapy, preferably an AI as opposed to tamoxifen, is being used.

Surgery to the Axilla

Recent pivotal studies have revolutionised the application of the time-honoured axillary lymph node dissection (ALND) as surgical treatment to the clinically node negative axilla. The Z011 trial randomised patients with positive sentinel lymph node biopsy (SLNB) following breast conserving surgery and receiving postoperative whole breast irradiation and adjuvant endocrine therapy (for ER+ tumours) to proceed to ALND or no further axillary treatment [Giuliano]. Omitting ALND did not show an inferior survival. In the AMAROS trial where patients with positive SLNB were randomised to receive either ALND or radiotherapy to the axilla, showing no difference in recurrence or survival, but the omission of surgery was associated with a significantly lower incidence of lymphoedema [Donker]. The use of preoperative ultrasound assessment, a widely practised standard of care in the UK, coupled with the use of SLNB, means that for those patients undergoing SLNB (implying a negative preoperative axilla on imaging with or without needle cytology or biopsy), the chance of finding a huge tumour burden in the remaining axilla is expected to be even lower than as shown in these trials. As a result, a number of national and international guidelines have changed advocating the omission of axillary treatments, including ALND and even SLNB in selected cases [Coates 2015, Lyman, Association]. In contrast to the trials mentioned above in relation to primary endocrine therapy versus surgery to the breast primary, these trials investigating axillary treatments were not specific to the older population. Given the argument in terms of differing biology with a higher chance of ER+ and rich tumours in the older adults, it is not difficult to imagine that the proposed approach to *all* patients as per these changing guidelines should be even more applicable to the older population.

Other Factors to Consider and Future Directions

When compared to their younger counterparts, older adults have shorter life expectancy due to co-morbidities or competing causes of death [Yancik, Ramsdale]. None of the above studies demonstrate any impact on survival with the use of 'less' surgery, which however has been shown to be beneficial in terms of local control in the cases of treating the primary tumours [Hind, Morgan, Chakrabarti, Johnston]. This effect however may be offset if the life expectancy of the person is reduced. Our work shows that the median time to progression for primary endocrine therapy using anastrozole was around five years as compared to approximately four years for tamoxifen, regardless of ER H-score (as long as it was ≥50) [Syed 2014]. More potent and novel endocrine agents continue to be developed. Fulvestrant, a selective ER down-regulator, has recently been shown in a phase 3 trial to be significantly more efficacious than anastrozole when used in advanced BC [Roberston]. Based on all these factors, primary endocrine therapy with a more potent agent, if used in an older adult with shortened life expectancy due to co-morbidities, and a very strongly ER+ tumour, may produce the optimal outcome in terms of local control, survival and health-related quality of life (HRQoL). The same principles should apply to the selection for axillary surgery. Future research should also aim to personalise treatments (surgery or no or 'less' surgery) taking full account of both biological (e.g. biomarkers other than ER, exploiting other techniques such as genomics) and geriatric (e.g. frailty, patient choice) [Hubbard] information into consideration.

RADIOTHERAPY

Radiotherapy in older BC patients follows much less standard guidelines than in younger ones, and is omitted in 40% after 75 [Schonberg, Biganzoli 2012, Hoffe].

Radiotherapy omission

Some authors have investigated the possibility to omit it after breast conserving surgery in older patients, in ER+ cases with very good prognosis [Hughes]. With long follow-up beyond 10 years, they have reported that although radiotherapy decreases local and regional relapse, it does not impact on OS in these patients aged 70 and above. This is in partial agreement with the Oxford overview which has shown an OS benefit of locoregional radiotherapy, observed as early as from 5 years of follow up, but in the general adult population. Therefore, omitting adjuvant radiotherapy after breast conserving surgery in older patients with small tumours and very good prognosis has been adopted by important guidelines as the NCCN. However, it remains debated and attitudes vary greatly across countries. The psychological burden of local recurrence should not be neglected, and compliance to endocrine therapy should be closely monitored. When considered, final decision to omit adjuvant radiotherapy should always take into account an estimate of life expectancy.

Innovations

The International Society of Geriatric Oncology (SIOG) recommends tailoring radiotherapy to patients using specific techniques and schedules modalities that will minimize toxicities without reducing effectiveness: position (lateral or prone), volume (partial), once-per-week fractionation, accelerated partial breast irradiation (PBI) [Kunkler].

Hypofractionated schedules are validated and provide good alternatives to standard fractionation, sparing expensive and burdensome transportations, especially in case of long distance from home [Fast, Kirova].

Potential advantages of accelerated PBI include shorter treatment time, improved cosmesis, and cost reduction compared with standard whole breast radiotherapy (e.g. IMPORT trial [Coles]). Intensity-modulated radiotherapy (IMRT) has the theoretical advantage of a further increase in dose conformity compared with 3-dimensional techniques, with increased normal tissue sparing, with potential benefit in older patients [Meattini]. This is particularly important since age >70 years seems to be one of the most significant factor for the occurrence of ischemic heart disease induced by radiotherapy [Darby].

Moreover, according to the BASO-II trial [Blamey], patients treated with either exclusive adjuvant radiotherapy or endocrine therapy show the same low yearly locoregional relapse rate (0.8%). This questions the systematic use of both strategies in very good prognosis cases, especially for older patients in whom mostly HRQoL drives treatment's choice, making patient's information crucial to avoid compliance issues observed with extended endocrine treatment or burdensome transportations with radiotherapy.

SYSTEMIC TREATMENT

Systemic treatment for early-stage BC must be interpreted in the context of the important effort led to identify sub-groups of tumours with different prognosis according to in-depth biology. Since the shift in treatment decision from prognosis to prediction which happened during the first 2000 decade, treatments have evolved towards more personalization combining both aspects [Curigliano]. One now considers treatments relying first on several biological features, expression of hormonal receptors [ER and progesterone receptors (PgR)] and HER2, distinguishing roughly 3 groups: luminal cases (ER+ and/or PgR+), triple negative tumours (ER-, PgR-, and HER2-) and HER2+ disease (overexpression of HER2 by IHC or amplified by F(C)ISH). The proliferation rate (e.g. Ki67) is used to differentiate further luminal cases that are aggressive from others, knowing that its optimal threshold (around 20-25%) is still a matter of debate.

Based on this evolving strategy, priority systemic treatments match all these categories: endocrine therapy for luminal cases, chemotherapy for triple negative tumours and when proliferation is considered as high, anti-HER2 treatments for HER2+ tumours but combined with chemotherapy as a standard since the benefit seems to derive from a high synergism between both classes of compounds.
In the general population, all these “priority” treatment modalities can be combined, either out of principle (e.g. anti-HER2 treatment and chemotherapy) or because of the benefit that can be expected from the different actions (e.g. chemotherapy if more than 3 lymph nodes involved in addition to endocrine therapy in ER+ and/or PgR+ tumours).

However, in adjuvant setting, treatments are applied blindly post-operatively based on a risk estimate summarizing the delicate trade-off between benefit sought through treatment (correction of a risk of relapse and death) and potential side effects. By essence, the long-term projections of benefit for such strategy aiming at postponing as much and as late as possible - if not cancelling - the risk of relapse collides bluntly with the list of comorbidities and competing risk for mortalities, all increasing in incidence and in severity with ageing [Kendal, Piccirillo, Ramsdale].
One can look at each systemic treatment modality.

Endocrine therapy

Given the clear gradual increase of the proportion of luminal cases according to age [Jenkins], most of older patients are beforehand candidates for adjuvant endocrine therapy. The historical debate between AI versus anti-oestrogen (tamoxifen) is over. Although there is a small additional benefit on disease-free survival (DFS) favouring AI, the true impact on OS is limited to 1 or 2 trials, stressing the need to pay attention first and foremost to side effects to ensure good compliance and regular intake. Indeed older patients with bone and joints disease are more at risk of stopping treatment with increased arthralgias and fractures as reported with the use of AIs [Coates 2007]. Risk of side effects or poor compliance may be worsened after an ALND or even a SLND, in those with a carpal tunnel syndrome or with severe osteoporosis. On the other hand, decreased functionality with low mobility may expose to a higher risk of thromboembolic events, more frequent with anti-oestrogen as tamoxifene.

Chemotherapy

Key cytotoxic agents in BC management are more difficult to handle in older patients because of the higher risk of side-effects: congestive heart failure with anthracyclines [Swain 2003], peripheral neurotoxicity and taxanes [Biganzoli 2016], myelosuppression with most cytotoxic agents requiring a wider use of G-CSF for primary prophylaxis of febrile neutropenia [Biganzoli 2012]. Adjuvant chemotherapy can provide similar benefits in older patients than in younger ones, but the risk of toxicity is higher, including fatal events (x10), and should be cautiously monitored [Muss 2005]. This is also why selecting cases relevant for such strategy is crucial, especially since so few patients older than 65 have been included in most trials of adjuvant chemotherapy, preventing from drawing any solid conclusion, and breaking the usual implemented misconception of the extrapolation of data obtained in younger patients to older ones.

Chemotherapy is clearly beneficial in patients with ER- disease, with up to 25% mortality (BC specific and global) reduction and an early effect, at 2-3 years when relapse peaks. Therefore it should be always considered for ER- disease, even in older patients, after careful general evaluation. This has been very well highlighted in retrospective works on large series where benefit vanishes as soon as the ER- population is mixed with the ER+ one [Elkin, Giordano], as well as in prospective trials as the CALGB 49907 where there was a high interaction between ER status and the efficacy of standard chemotherapy [Muss 2009].
Validated regimens are fuddy-duddy and include 4 cycles of doxorubicin/cyclophosphamide (AC) and the old

cyclophosphamide/methotrexate/fluorouracil (CMF) [Muss 2009], or 4 cycles of docetaxel/cyclophosphamide (TC) [Jones 2009]. Sequential schedules (anthracyclines followed by taxanes) have never been rightly investigated after 65 years, and usually double the length of chemotherapy period which is highly influential on the risk of serious side effects as identified in the last work led by late Arti Hurria [Hurria], reflecting the decline of functional reserves with age.

For chemotherapy, the main question mark remains whether selected patients with ER+ disease may derive some additional benefit from chemotherapy without triggering high rates of side effects and jeopardizing the whole therapeutic plan. This explains why so much expectation has been put in multiparametric tests assessing the in-depth biology of the tumour with genome profiling. However, despite large trials with number of patients often exceeding 5,000 each, none has been led consistently with accrual closed to patients aged 65 and above, making the extrapolation of the use of such signatures in older patients from the data obtained in younger ones very theoretical and inadequate. A solution could be to factor part of the age-linked heterogeneity and competing risks in these algorithms. More recent research, as the ASTER 70s randomized phase III, addresses this issue and might help in the future fine tuning indications of chemotherapy for ER+ BC in older patients [Coussy 2016]. Until this happens, adjuvant chemotherapy for ER+ BC patients above 65-70 should be considered only as optional and in a very limited number of cases, endocrine treatment bringing already an important benefit.

Anti-HER2 treatments

Despite accounting for 40% of BC patients, few older women have been included in pivotal trials: only 16% of patients in the key studies of adjuvant trastuzumab were 60 and above. Trastuzumab, pertuzumab and neratinib are all approved for (neo) adjuvant therapy.

The benefit of adding trastuzumab to adjuvant chemotherapy is independent of age as shown in most large adjuvant trials like HERA [Cameron]. Attempts to use anthracyclines-free regimen potentially decreasing the cardiac risk as in the BCIRG 006 with docetaxel and carboplatin (TCH regimen) cannot be considered valid in the older population which was excluded from the trial [Slamon].

Indeed, establishing the standard adjuvant trastuzumab regimen in older patients is difficult since the accompanying chemotherapy remains poorly defined. Data are lacking for sequential chemotherapy, leaving us with the old-fashioned 4 AC, 6 CMF, and 4 TC. The attractive results from a single-arm study led in patients with low risk HER2+ node-negative BC with weekly paclitaxel x12 and trastuzumab have opened by extrapolation such use for older ones, but with a very low level of evidence and the risk of neuropathy [Tolaney].

Although most trials of short-duration trastuzumab (6 months or 9 weeks versus 1 year) failed to show the non-inferiority of shorter duration, PERSEPHONE did find that 6 months trastuzumab was non-inferior to 12 months [Earl]. Some subgroup analysis suggests also that patients with small node-negative tumours would not derive extra benefit from extending trastuzumab beyond 6 months [Kramar].These studies showing lower rate of cardiac dysfunction with the shorter duration arm, shorter duration might be relevant in older patients at increased cardiac risk.

Of note, data from the Surveillance, Epidemiology and End Results (SEER) registry show that patients >65, especially octogenarians and those with comorbidities, often

receive incomplete (≤ 9 months) treatment [Vaz-Luiz], whether related to the chemotherapy partner or to the antibody. Delay or cessation was seen in 15-40% of cases. Thirty percent of patients developed an LVEF decrease ≥10%, and 3-11% were hospitalized for cardiac events within 1-2 years of follow up.

As oral formulation for chemotherapy, subcutaneous trastuzumab would help older patients avoid the need to travel to hospital if approved for administration at home. Although approved for extended treatment after trastuzumab, neratinib, an irreversible TKI of HER1, HER2 and HER4, gives more than 40% of grade 3-4 diarrhoea making it unlikely such a strategy will suit the general older population [Chan].

Dual blockade with pertuzumab (or lapatinib) and trastuzumab is another attractive innovative strategy [von Minckwitz]. Disappointingly, studies exploring this concept had no greater success than previous ones in enrolling patients >65. Moreover, to the issues of selecting the right chemotherapy partner and controlling the increased risk of side-effects, dual blockade adds the difficult selection of older patients according to frailty status for a modest absolute benefit.

Actually the crucial research question remains whether HER2+ BC can be adequately treated by adjuvant anti-HER2 therapy alone, as suggested by the randomized Japanese study (RESPECT) [Sawaki].

Table 1 summarizes some of the key points regarding adjuvant chemotherapy and anti-HER2 treatment in older early-stage BC patients, based on SIOG recommendations [Biganzoli, Brain].

TABLE 1. Summary of key points on chemotherapy and anti-HER2 treatment in older early-stage BC patients

CHEMOTHERAPY	
Indications	Focus on ER- and HER2+ tumours if pT> 5 mm
Regimens	
4 AC (or 6 CMF), 4 TC	Validated
Weekly paclitaxel x 12	Option?
Liposomal doxorubicin	Potential interest (lower cardiac toxicity) but no data
"Sequential" chemotherapy (anthracyclines and taxanes)	No data
Capecitabine or docetaxel weekly	No indication
Primary prophylaxis of febrile neutropenia with G-CSF	From a lower threshold of risk of febrile neutropenia than the standard one used in the adult population (20%)
TRASTUZUMAB	
Indications	No restriction if chemotherapy indicated
Regimens	
4 TC + trastuzumab	Most validated
Weekly paclitaxel x 12 + trastuzumab (Tolaney)	Option
TCH x 6	Very unlikely in older patients since

	carboplatin AUC 6!
Trastuzumab without chemotherapy	Can be considered, especially for unfit patients (+ endocrine therapy in the case of ER+ tumours)
Duration	1 year Shorter duration (6 months) may be considered in small node-negative tumours or in patients at increased cardiac risk

Neoadjuvant strategy

The neoadjuvant approach in older patients can be difficult since this strategy generally involves chemotherapy rather than endocrine treatment, possibly jeopardizing subsequent surgery by causing a deterioration of health status. However, as discussed previously in the surgery section, primary endocrine therapy may be a good alternative to upfront surgery. It allows also exploring new treatments and selection processes, enabling investigating strategies omitting aggressive treatments as chemotherapy through multiple blockade of the HER2 and associated pathways such as ER.

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