

Breast cancer in the elderly: different treatment modalities

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As for most malignancies, breast cancer (BC) incidence increases with age from 1 in 209 for women younger than 40 to 1 in 14 for women over the age of 70 years old; in the UK one third of BCs affect patients aged ≥ 70 years.

Despite the increase in the elderly population, the safety, efficacy and necessity of therapeutic modalities in very elderly BC patients remain under-studied. Studies have demonstrated that older patients are less likely to receive standard care for BC. Furthermore, the mortality rates for these patients in the last few decades have shown modest improvements compared with younger patients, suggesting that comprehensive, state-of-the-art, care is compromised. As elderly women have historically been excluded from prospective clinical trials, treatment guidelines are usually based on results of studies in a younger population. Nevertheless, recent studies have looked specifically into treatment options and outcomes for this age sub-group; this novel approach is summarised here, bearing in mind that patients' priorities and therapeutic targets might need to be readjusted and personalised in older women with BC.

Endocrine treatment

In the 1980s Primary Endocrine Treatment with tamoxifen was first suggested by Scottish researchers [1]. This idea rapidly gained in popularity as several trials demonstrated that there was no survival disadvantage to omission of surgery in women >70 . Whilst local control rates were inferior, even long-term follow-up showed little detriment in overall survival with only one of the trials showing a slight, but significant improvement in survival with surgery. A meta-analysis of all studies conclusively demonstrated only a small, non-significant trend for improved survival with surgery which is nevertheless associated with a significant gain in local control [2]. Limited compliance with medical treatment and issues of multi-drug resistance should also be taken into account in treatment planning.

For the very frail woman, for whom BC may pose a reduced threat to life, and for whom its treatment may be associated with increased risk, tailored endocrine strategies may be appropriate: surgery may be minimised or even avoided without detriment to BC outcomes.

As the effectiveness of hormonal treatment in the frequent cases of ER+/PgR+ in older BC patients is indubitable, the use of primary endocrine treatment (PET) is often an option when patients are asking for breast-sparing surgery. A course of 2–4 months of PET also allows optimisation of the patient's general condition: improved nutrition, fluid and electrolyte re-balance, correction of anaemia and psychological adjustment play important roles in reducing surgical morbidity a few months after the cancer has been diagnosed and treated with hormonal manipulation.

Despite aromatase inhibitors having been on the market for over a decade, a clear advantage in survival rates has not been demonstrated. Side effects and toxicities should then be taken into account: it is for this reason that there is still a role for tamoxifen as an option for patients with severe osteopenia. Recent prospective investigations in younger patients have demonstrated a DFS and OS advantage when treatment was switched after 2–3 years from tamoxifen to aromatase inhibitors.

Surgery

Breast cancer surgery is associated with a very modest risk of operative morbidity and mortality. Wherever feasible, older women with a reasonable life expectancy should be treated with standard surgical procedures applicable to younger patients, including the choice of breast conservation or mastectomy where appropriate; breast reconstruction or oncoplastic procedures should be included in the options available [3].

A quick general anaesthesia is usually well tolerated and is preferable to local anaesthetic or loco-regional blocks. Specific situations should be discussed jointly

between anaesthetists, geriatricians and surgical oncologists. Frailty assessment tools may assist in treatment planning as they are associated with surgical outcomes [4].

Sentinel node biopsy has further reduced the extent and length of surgery and simplified the postoperative course and wound management. A clear advantage in axillary clearance has been debated in this age group, with some studies showing no benefit in N0 patients [5]. Occasionally, when the operative risk is above average, the decision to avoid sentinel node biopsy and conduct a low level axillary dissection at the time of primary surgery could be an option.

The patient's preference is often an issue: older BC patients and their relatives should be clearly reassured that surgery is not overwhelming and can often be delivered as a day-patient, the operative pathway is not excruciatingly painful and anaesthesia can be safely delivered at advanced ages. The use of no drains often facilitates postoperative management and early discharge.

With the expansion of life expectancy and specifically of healthy life expectancy, more senior patients enjoy an excellent quality of life even at a very advanced age, often engaging in social and leisure activities. It is thus not surprising that older BC patients seek improved cosmetic outcomes. Breast gland remodelling and even breast reconstruction, is thus becoming an issue, with several series reporting increasing numbers [6].

Chemotherapy

Data from prospective trials specifically addressing adjuvant BC therapy in an older population are limited. The SIOG (International Society of Geriatric Oncology) recommendations [7] stated that treatment with adjuvant chemotherapy should not be an age-based decision, but, instead, should take into account individual patients' estimated absolute benefit, life expectancy, treatment tolerance and preference.

Older N+, ER+/PgR+ BC patients potentially derive the largest benefit in survival gain. In the absence of cardiac contraindications, four courses of an anthracycline-containing regimen are usually preferred over CMF in elderly patients with BC. Taxanes could be added to anthracyclines in high-risk, fit elderly women. Docetaxel and cyclophosphamide or CMF can replace anthracyclines in patients at cardiac risk. In the absence of cardiac risk, adjuvant trastuzumab should be offered to older patients with *ERBB2*-positive BC when chemotherapy is indicated, but cardiac monitoring is essential.

Since then, investigations have confirmed that adjuvant taxotere and cyclophosphamide (TC) chemotherapy can be safely administered as adjuvant treatment in BC patients >70 years with long residual life expectancy and no major co-morbidities [8]. Prophylactic G-CSF was often administered (mostly from the first cycle) to support an optimal delivery of chemotherapy. Neutropenia was reported in 15% of patients, including febrile neutropenia and/or grade 4 in 5% for each. Interestingly, this study reported the results of geriatric assessment, allowing a much better understanding of the frailty status. It appears more and more evident that co-morbidity is not the sole factor to be considered in the treatment planning process. Frailty assessment increased the understanding of compliance with medical treatment (chemotherapy) [9]. Both inferior MNA (nutrition) and MMSE (cognition) scores increased the probability non-completion of chemotherapy. Also, an inferior score for MNA and GFI showed an increased mortality risk after the start of chemotherapy. The mean MMSE score worsened significantly during chemotherapy.

Comprehensive Geriatric Assessment (CGA), including functional, cognitive, social, psychological and nutritional status as well as poly-pharmacy, is more frequently being adopted [8]. CGA has been shown to predict chemotherapy toxicity [10]. Unfortunately, the lack of geriatricians and the time needed for CGA completion make its routine use in onco-geriatric series slightly impractical. Not surprisingly, most onco-geriatric evaluations are being conducted by the treating physicians (medical/surgical oncologists). The use of quick screening tools (i.e. VES-13, GFI, TUG, etc.) is highly recommended as a first necessary step, which will allow those individuals requiring full implementation of CGA to be identified (if GFI ≥ 4 or VES13 ≥ 3).

Results suggest that age remains an independent variable associated with a decreased use of adjuvant chemotherapy. Systemic adjuvant chemotherapy remains underused in "fit" patients. Further efforts are needed to better integrate CGA into tumour board proposals for older patients with early breast cancer [11].

Radiotherapy

Tolerability is not a limiting factor for radiotherapy in older patients in terms of toxicity [12,13]. An 11% absolute reduction in five-year local recurrence after breast-conserving surgery has been noticed in the >70-year-old age group [14].

The decision to offer radiotherapy is to be based on patient health and functional status, risks of mortality from comorbidities (particularly cardiac and vascular) and risks of local recurrence. Compliance is also an important issue, with several patients dropping out due to lack of logistics, social support and transportation. It is for this reason that we are looking with utmost interest to the future findings on intraoperative irradiation, which is particularly relevant to the onco-geriatric population.

Post-mastectomy chest-wall irradiation is indicated if patients have ≥ 4 involved nodes or a T3–T4 tumour. In older patients with a life expectancy of less than five years, the decision to implement adjuvant radiotherapy should be based on considerations of locoregional control alone.

Metastatic disease

A French retrospective investigation on metastatic breast cancer (MBC) revealed that the cut-off point at which therapeutic decisions are affected by age is 76.5 years; a marked decrease in the prescription of reference chemotherapy in MBC patients was noticed after this threshold [15]. Data on the benefit of chemotherapy in MBC patients aged ≥ 75 years, are very limited [16]. No randomised studies comparing the best supportive care and chemotherapy have been published in this setting. Most studies focus on the efficacy and tolerability of a specific type of chemotherapy and no retrospective analyses of cohorts of elderly patients receiving a range of treatments have been published. Less than 40 scientific articles report on the use of chemotherapy for elderly patients with metastatic BC [17]. A French study group recently revisited their institutional series and reported 56% alive at one year and 25% at two years, providing encouraging survival for elderly patients with endocrine-resistant metastatic BC. Capecitabine effective (1000 mg/m² twice daily) side effects were: 3% grade 4 diarrhoea, 8% grade 3 hand-foot syndrome, 3% grade 3/4 mucositis, 13% grade 2 hand-foot syndrome, 4% grade 2 diarrhoea, 6% grade 2 asthenia. On the other hand, 25% deaths occurred within three months of initiation of chemotherapy, confirming the absolute need for geriatric assessment before initiation of treatment, even if PS is a highly significant prognostic factor both for progression-free survival and overall survival.

Final considerations and future projects

Effective communication of cancer diagnosis and treatment planning is known to be the key to optimal

health outcomes. Health care professionals frequently lack the communication skills needed to identify patients' individual concerns and problems. As a consequence, the information provided is frequently insufficiently tailored to the patients' needs [18]. Older patients seem to have less prominent needs for communication regarding the effect of cancer treatment on sexuality, body appearance and for psychosocial support than younger patients. They want to receive relevant information about the treatment, but are relatively less interested in extensive and detailed information. Evidence is being collected to prove how older cancer patients are better able to regulate their emotions and cope with illness than younger ones.

Communication training for dedicated nurses regarding cancer-specific and generic issues has been investigated [19]; the success of these specific training programmes anticipates the role of and need for specialised onco-geriatric nurses.

More elderly patients need to be entered into clinical trials; they represent 22% of trial enrollees, compared with 58% of the Canadian population with cancer [20]. More specifically for breast cancer, the accrual is 18% in Canada (NCIC) and 9% in the USA (SWOG).

Age remains a barrier for accrual into clinical trials, even when reimbursement is not an issue. strategies are to be put in place to overcome this barrier, bearing in mind that the greatest impediment to enrolling older women in clinical trials is physicians' perceptions about age and tolerance of toxicity [21].

The results of dedicated trials will assist in defining standards of care, provided that frailty assessment is constantly being utilised, in order to clarify the general conditions of onco-geriatric patients. A great degree of flexibility and adaptation should always be considered when counselling older BC patients and advising on treatment.

Conflict of interest statement

The author has no financial and personal relationships with other people or organisations that could inappropriately influence/bias his work.

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