Triple-negative breast cancer in the older population

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Breast cancer in advanced age has been associated with a slightly increased probability of favourable tumour biology (e.g. hormone receptor-positive and human epidermal growth factor-2 [HER2]-negative by immunohistochemistry). Nevertheless, a substantial proportion of older women (~15–18%) still develop ‘triple-negative’ breast cancer (TNBC), which is generally associated with a poor prognosis. To date, there have been very few investigations comparing the prognosis of younger and older women with TNBC; however, some emerging studies suggest that older patients with TNBC may have a better outcome when compared with their younger counterparts. The reasons for these differences in prognosis have yet to be fully elucidated, but may be due to age-related biological variations, as suggested by observed differences in the distribution of histological subtypes of TNBC, or perhaps other unknown (biological) factors. Despite the evidence of benefit of chemotherapy in TNBC in older women, there is still a tendency for geriatric patients to receive less adjuvant chemotherapy than their younger counterparts.

Key words: chemotherapy, elderly, geriatric, prognosis, treatment, triple-negative breast cancer

introduction: occurrence of ‘triple-negative’ breast cancer in the older population

Breast cancer is the most common tumour in women, and 21% of cases occur in those older than 70 years [1]. Advanced age at the time of breast cancer diagnosis has been associated with a slightly increased probability of favourable tumour biology, with node-negative, hormone receptor (HR)-positive, and human epidermal growth factor-2 (HER2)-negative breast cancers being found somewhat more frequently in older women [2–4].

Nevertheless, a substantial proportion of older women still develop ‘triple-negative’ breast cancer (TNBC), which does not express oestrogen receptor (ER), progesterone receptor, or overexpress HER2, and is generally associated with a poor prognosis [2]. A recent review from the United States estimated that ~15% of breast cancers in older patients are TNBC, and in a study from the Shanghai Cancer Hospital, TNBC represented 18.4% of all breast cancers in patients aged ≥70 years [5].

Recent studies have started to investigate the distribution of different histological subtypes among older patients with TNBC. Most recently, an analysis of 563 TNBC patients from the UH Leuven database demonstrated a statistically significant link between age and histological subtype [6]. In this study, triple-negative apocrine or lobular carcinomas occurred substantially more often in older individuals, compared with the most common subtype, invasive ductal carcinoma not otherwise specified (IDC-NOS) [6]. Age-related differences in the distribution of histological subtypes in TNBC might partly explain age-specific differences in prognosis.

prognosis in older patients with TNBC

Younger age is generally associated with poorer prognosis when considering all forms of breast cancer, and this may be partly related to variation in the distribution of biological subtypes encountered in different age groups. To date, there are few studies comparing the prognosis of younger and older women with specific breast cancer subtypes, including TNBC. Remarkably, three recent studies suggest that older patients with TNBC may have a better or equivalent outcome when compared with their younger counterparts. In a retrospective analysis, Cheung et al. [7] identified a similar rate of 5-year survival and local/regional recurrence after surgery in older (aged ≥70 years; n = 127) and younger (n = 342) patients with invasive TNBC, despite the older age group having not received adjuvant chemotherapy [6]. Thike et al. [8] used multivariate regression analysis to search for correlates of disease-free survival (DFS) and overall survival (OS) in 653 patients with basal-like TNBC [8]. Younger age, defined as less than the mean age of the study population (53 years), was found to be strongly correlated with shorter DFS and OS (P = 0.033 and 0.001) [8]. Finally, a similar analysis was performed on 308 patients with triple-negative IDC-NOS, the most frequent subtype of TNBC, which was found in 80% of the TNBC patients sampled in the study [6, 8]. This investigation, which excluded the more rare histological subtypes of TNBC (which can sometimes have inherently different prognoses to IDC-NOS), found that DFS was worse in older individuals, but, when corrected for the use of
adjuvant chemotherapy and radiotherapy, was significantly better for the older population (hazard ratio per 10-year increase in age = 0.68 [95% confidence interval (CI) 0.52–0.89]) [6, 8].

There is no clear explanation for the aforementioned correlation between younger age and decreased DFS and OS in patients with TNBC. It might be related to differences in tumour biology, as suggested by a different distribution of histological subtypes, although other biological factors could also be present. For instance, BRCA mutations are more frequent in the young, and are often associated with TNBC [9, 10]. Differences in treatment might also be involved, but this is counterintuitive, as older patients are less likely to be treated according to the accepted treatment guidelines [3, 4], which is likely to have a bearing on prognosis. Undertreatment in older patients with breast cancer is known to have a strong negative effect on survival [3, 4, 11], and the International Society of Geriatric Oncology (SIOG) recommends that surgery, adjuvant radiotherapy and systemic therapy should not be denied to breast cancer patients on the basis of age alone [12].

adjuvant therapy for TNBC in older patients
The SIOG guidelines recommend that chemotherapy should not be an age-based decision. Instead, the decision to start chemotherapy should be based on an individual’s estimated absolute benefit, life expectancy, treatment tolerance and preference [3, 4]. A retrospective study by the Cancer and Leukaemia Group B (CALGB) found that older and younger women derived similar reductions in breast cancer mortality and recurrence from regimens containing more chemotherapy (i.e. chemotherapy regimens containing a greater number of agents, or a higher dose of agents) [13]. This large retrospective evaluation of nearly 6500 patients provided initial evidence that age should not be a barrier to intensive regimens of chemotherapy if patients are in good health.

Several studies have indicated that older patients with HR-negative tumours benefit significantly from adjuvant chemotherapy. The Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) meta-analysis on the effect of chemotherapy (cyclophosphamide, methotrexate and fluorouracil; CMF) in post-menopausal women aged 50–69 years with ‘ER-poor’ tumours found a 6% reduction in 10-year breast cancer mortality; however, almost no data were available for women aged ≥ 70 years [14]. Two retrospective studies with the Surveillance, Epidemiology and End Results (SEER) database have demonstrated that adjuvant chemotherapy improves OS in geriatric patients aged ≥ 70 years with ER-negative tumours [15, 16]. A prospective randomised study conducted by CALGB found that standard chemotherapy (either CMF or doxorubicin and cyclophosphamide [AC]) was superior to capecitabine as adjuvant chemotherapy in older women (aged ≥ 65 years) with early-stage breast cancer, an effect that was most pronounced in women with HR-negative tumours [17]. Finally, in a small subset analysis of older French women (≥65 years; N = 338), patients with HR-negative tumours treated with weekly epirubicin plus tamoxifen were found to have a significantly greater 6-year DFS, compared with those treated with tamoxifen alone [18].

Anthracyclines are a cornerstone of adjuvant chemotherapy for breast cancer, but there are concerns of cardiac toxicity, which can have an important impact on quality of life and survival. A study with the SEER database showed that the 10-year incidence of cardiac failure in women aged 66–70 years was as much as 38% in patients treated with adjuvant anthracyclines, compared with 28% in those without adjuvant chemotherapy (although no substantial difference was observed in patients aged 71–80 years) [19]. Non-anthracycline regimens (such as docetaxel and cyclophosphamide [TC]) have been studied and can be utilised without intrinsic cardiac risk for older women [20]. Following a phase III trial involving 510 women with operable stage I–III breast cancer (stratified by HR and HER2 subtype), Jones et al. [20] compared the effects of TC versus AC in a subset analysis of older (≥65 years) and younger women. TC was found to be associated with a more favourable DFS and OS than AC in both age groups, including patients with either HR-negative or HER2-negative tumours [20]. TC was well tolerated in the trial, with low levels of febrile neutropenia observed in older patients (8%), which might have been due to the recommended (but not compulsory) use of prophylactic antibiotics. Other studies have shown higher rates of febrile neutropenia with TC, and the prophylactic use of granulocyte colony-stimulating factor could be considered with this regimen in some older individuals, as suggested by the European Organisation for Research and Treatment of Cancer in 2011 [21], but not in all cases [22, 23].

treating metastatic TNBC in older patients
In general, older patients with metastatic breast cancer are expected to derive similar benefits from chemotherapy (in terms of response and delay of progression) as younger patients [3, 4, 24]. Monotherapy is generally preferred, as combination therapy is often associated with increased toxic effects, while OS is generally not affected [3, 4].

Existing evidence suggests that most drugs used in the young can also be used in the old; however, randomised investigations in older populations are few in number, and do not always stratify patients according to HR or HER2 status. A phase III trial involving older women (≥60 years) with metastatic breast cancer found that epirubicin was generally well tolerated and statistically superior to gemcitabine in terms of time to progression and OS [25], indicating that anthracyclines can be a valuable option in advanced patients of old age. In cases where anthracyclines are considered but concerns about cardiotoxicity exist, liposomal formulations that prolong infusion times could be used to minimise cardiotoxicity [26]. Several studies have also explored the use of taxane-containing regimens, supporting the view that weekly taxanes are a reasonable consideration for older patients with metastatic breast cancer [27]. Similarly, the efficacy of capecitabine has also been established in prospective and retrospective studies in older women with metastatic breast cancer, and is a commonly used treatment in such patients [28, 29]. Capecitabine is known to be generally well tolerated in geriatric populations; however, dose modification based on close monitoring of renal function, which is often diminished in older patients, is imperative [30].
It should be noted that it is not possible to provide strict guidelines on which agents to use for TNBC in older patients. As treatment in this setting is palliative, any treatment regimen should consider quality of life, and substantial toxic effect is not acceptable. Paclitaxel and vinorelbine are not the first choice in patients with diabetes or peripheral neuropathy, capecitabine and methotrexate should be used cautiously and with dose reduction in cases of reduced renal function, and classical anthracyclines should be avoided in patients with cardiovascular risk functions [24].

Metronomic chemotherapy, initially devised for paediatric contexts, is gaining increasing recognition as a regimen for geriatric breast cancer patients [31–33], given the low number of subjective side effects, and observations of reasonable effectiveness. Such regimens typically consist of methotrexate (2.5 mg given twice daily, for 2 consecutive days each week) with cyclophosphamide (50 mg/day) [31–33]. DNA damaging agents such as cisplatin and cyclophosphamide have been linked to important clinical activity in TNBC; however, to date there are no randomised data available to allow the comparison of metronomic regimens with more classical regimens of chemotherapy, nor to establish if they are of particular benefit in TNBC.

Targeted therapies for the treatment of metastatic TNBC are starting to emerge. Currently, the anti-angiogenic agent bevacizumab is the only targeted therapy for HER2-negative breast cancer registered for use in Europe, and has been shown to increase progression-free survival (PFS) but not OS in combination with paclitaxel [34]. A subset analysis of three phase III trials demonstrated that TNBC patients also benefit from increased PFS following the addition of bevacizumab to chemotherapy [35]. The authors of a subpopulation analysis of the ATHENA study reported that bevacizumab plus paclitaxel provided a median PFS of 10.4 months (95% CI 8.8–11.8) in patients aged ≥ 70 years [36], a figure comparable with that reported in the original study population (9.5 months [95% CI 9.1–9.9]) [37], and in the E2100 trial (11.8 months) [34]. In this sub-analysis, older patients had an increased rate of hypertension and proteinuria compared with their younger counterparts, but otherwise demonstrated a comparable toxic effect profile [36]. Although bevacizumab was generally well tolerated in this study [36], it is known to have rare yet severe side effects, such as cardiac failure, and arterial and venous thrombotic events, to which non-fit geriatric patients (who are generally not included in clinical trials) are probably more vulnerable. The discussion on the cost–benefit and optimal use of bevacizumab in metastatic breast cancer in still ongoing [38].

**conclusion**

TNBC makes up an important proportion of breast cancers in the older population. TNBC is generally aggressive, with a poor prognosis, but there might be some age-related biological differences, as suggested by observed differences in the distribution of TNBC subtypes, or perhaps other unknown biological factors. Older breast cancer patients tend to receive less adjuvant chemotherapy than their younger counterparts; however, there are several studies suggesting that such therapy provides benefit in older patients with TNBC. Much of this evidence is based on retrospective analyses, and there is a need for prospective clinical trials to evaluate anticancer therapeutics in older women. Many of the studies described to date have used varying age cut-offs to define the older population. Future investigations should aim to be more consistent in the demarcation of the older age group, which should help improve inter-study data comparison and our understanding of treatment requirements in this important demographic group.

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