

Updated recommendations regarding the management of older patients with breast cancer: a joint paper from the European Society of Breast Cancer Specialists (EUSOMA) and the International Society of Geriatric Oncology (SIOG)

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Summary

Breast cancer is increasingly prevalent in older adults in the context of ongoing demographic changes and is a significant part of routine oncology practice. Nonetheless, due to its highly heterogeneous nature, management of breast cancer in this population is challenging, with the validity of the available evidence very limited for older adults. Decision-making should not be driven by age alone but involve geriatric assessments plus careful consideration of life expectancy, competing risks of mortality, and patient preferences.

A multidisciplinary task force including members of the International Society of Geriatric Oncology (SIOG) and the European Society of Breast Cancer Specialists (EUSOMA) gathered to expand and update the previous 2012 evidence-based recommendations for the management of breast cancer in older individuals with the endorsement of the European Cancer Organisation. These were expanded to include chemotherapy toxicity prediction calculators, cultural and social considerations, surveillance imaging, genetic screening, genomic tools, neoadjuvant systemic treatment options, bone-modifying agents, targeted therapies and supportive care. Recommendations on geriatric assessment, ductal carcinoma in situ, screening, primary endocrine therapy, surgery, radiotherapy, adjuvant systemic therapy and secondary breast cancer were updated.

Introduction

Aging is the leading risk factor for cancer.(2) The prevalence of breast cancer (BC) in older adults is increasing and the higher cancer mortality in older adults compared with younger women establishes a major health disparity which may be explained by more advanced presentation, delayed diagnosis, organ function decline and multimorbidities.(3) Nonetheless, functional age (and not chronological age) and the potential underlying frailty should drive decision-making. Older patients are underrepresented in clinical trials which do not always enrol individuals more frequently seen in routine practice. Therefore, the risks and benefits of anticancer therapy should be carefully weighed.(4)

A multidisciplinary task force including specialists in medical oncology, radiation oncology, surgery, geriatrics, radiology and epidemiology and patient advocates affiliated with the International Society of Geriatric Oncology (SIOG) was created in 2007 to prepare recommendations for the management of BC in older individuals.(5) These were subsequently updated in 2012 in collaboration with the European Society of Breast Cancer Specialists (EUSOMA).(6) Here we present an update of the task force recommendations based on the new evidence which has become available since 2012 (Table 1). These recommendations are a consensus by an expert task force on available evidence and expert opinion.

Search strategy, selection criteria and grading of the evidence

Each task force expert performed a scoping literature review on Pubmed/Medline on individual topics pertaining to breast oncology (MeSH: “older” or “elderly” and “breast cancer” and “surgery”, “radiotherapy” or “systemic therapy”) and any updates available since the previous recommendations were published in April 2012. The list of topics included epidemiology, geriatric assessment, cultural and social considerations, genetic screening, ductal carcinoma in situ, screening, surveillance imaging, primary endocrine therapy, surgery, radiotherapy, adjuvant and neoadjuvant systemic therapy, genomic tools, treatment of secondary breast cancer, chemotherapy toxicity prediction, bone-modifying agents, targeted therapies and supportive care. The experts presented the results of each individual scoping review to the task force during various meetings held between February 2019 and August 2020. During these meetings, the need to update the previous recommendations was discussed and consensus reached by unanimity; the level of evidence was graded according to the four-classes classification proposed by the US Agency for Healthcare Research and Quality (AHRQ) and recently adopted by EUSOMA.(1)

General and worldwide concepts on ageing

Frailty involves decreased physiological and functional reserve leading to vulnerability to stressors and adverse outcomes. Stratififying patients as fit, vulnerable and frail may identify those at risk of complications.(7) Collaboration between cancer specialists and geriatricians and geriatric assessment (GA) are recommended. Frail individuals require tailored approaches based on a GA and focusing on supportive care. Fit individuals may tolerate standard treatment similarly to younger patients. Vulnerable individuals may require treatment adjustments and geriatric interventions. Competing mortality risks may justify less aggressive approaches. The National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) guidelines recommend evaluating life expectancy and calculators such as *ePrognosis* may aid in assessing whether cancer is likely to shorten it.(8, 9) Since competing mortality risks are more prevalent in older adults even without multimorbidities, treatment decisions should consider not only the risk of BC recurrence, but also the risk of dying of other causes, which is strongly influenced by frailty.

GA is a multidimensional evaluation aiming to determine physiologic age and guide diagnostic and therapeutic interventions targeting reversible deficits and devising treatment strategies to eliminate or mitigate them.(10) Increasing evidence supports the role of GA in the care of older patients with BC. The implementation of GA may improve tolerance, health-related quality of life (QoL) and satisfaction.(11-15) ASCO recommends GA for patients aged 65 years and older considered for chemotherapy.(8) GA can be time-consuming and may not be necessary for all older patients. Several screening tools (some self-reported) can identify patients requiring GA, and should be considered as the gateway to any cancer treatment decision-making in patients aged 70 and older.(16, 17)

The Cancer and Aging Research Group (CARG) and the Chemotherapy Risk Assessment Scale for High-age patients (CRASH) scores estimate the risk of grade 3-5 chemotherapy toxicity in older patients (Table 2) and were validated in cohorts including 20% of BC patients.(18, 19) A BC-specific risk score (CARG-Breast) has been developed and validated but is not yet available.(20) Chemotherapy toxicity calculators should be used as an adjunct in the decision-making process.(21) Multimorbidity and toxicity may influence treatment efficacy (especially endocrine therapy) as nonadherence increases with age.(22)

Cultural and social aspects, including religious myths and taboos, and patient values must be considered during diagnosis and treatment, especially in the context of the current migration flows. Older adults from immigrant populations may have more disabilities, worse self-rated health and poorer outcomes. Literacy and education are also heterogeneous and some assessment tools may not be universally applicable.

Mammography screening and surveillance

Screening

Most screening programs extend until 69-70 years and a minority until 74-75 years. The European Commission Initiative on Breast Cancer and the US Preventive Services Task Force recommend screening mammography for women aged 70–74 years despite the risk of over-diagnosis.(23, 24) A meta-analysis found a relative risk reduction for BC mortality of 0.80 for women aged 70–74 years,(25) although there is controversy also in younger patients. Screening every 2-3 years is deemed to provide the best balance between benefits and harms. The American Cancer Society recommends mammography in older women,(26) particularly in the

context of a life expectancy ≥ 10 years. However, screening is unlikely to be beneficial after age 75(24) and decisions should consider overall health and life expectancy.

Surveillance

No evidence supports the benefit of mammographic surveillance on disease-specific mortality for older BC survivors in the context of multimorbidities and competing mortality risks. The risk for ipsilateral recurrence and contralateral BCs over the age of 75 years is not defined and is influenced by tumour biology and adjuvant therapy.(27) International guidelines recommend indefinite annual mammography regardless of age.(9, 28) Annual or biennial mammography is recommended for women aged 70–80 years although multimorbidities, life expectancy and frailty should be considered.(27) It should be avoided in patients over 80 years with multimorbidities or life expectancy ≤ 5 years.(29)

Genetic screening and its implications

The prevalence of pathogenic variants associated with a germline BC predisposition is almost 3 times less over age 65 (5.6% vs 14.2%).(30) BRCA2 and CHEK2 have been found to be relatively prevalent in women aged over 65 with BC.(30) Nonetheless, they are less likely to undergo genetic testing, as guidelines often focus on younger populations. For older patients, genetic testing based on simple, cancer-based criteria may potentially deliver consistent, cost-effective and patient-centred outcomes. Selection of candidates appropriate for screening should be considered in line with current local and/or national guidelines.

In the curative setting, germline pathologic variant carriers may benefit from high-risk surveillance or risk-reducing interventions in the context of an adequate life expectancy.(9) Also, carriers should be offered cascade testing and evaluation of their relatives. For advanced disease, poly ADP-ribose polymerase (PARP) inhibition is a potential alternative to chemotherapy for older BRCA carriers, especially regarding QoL.(31)

Neoadjuvant systemic therapy

Fit older patients should be considered for neoadjuvant strategies similarly to their younger counterparts based on the clinical subtypes of the primary tumour.(32) Due to the higher risk of adverse outcomes,(33-35) vulnerable patients may be better served by upfront surgery,

particularly if BC is already operable. The likelihood of breast conservation should also be considered based on disease characteristics, expected response and patient preference. In fit older persons with high-grade triple negative BC (TNBC), optimal chemotherapy is still debated. Similarly to the adjuvant setting, sequential regimens with anthracyclines and taxanes may be considered although evidence is very limited and shorter regimens remain reasonable. Adding platinum compounds remains debated and may be challenging for most older adults.

Pathological response after neoadjuvant chemotherapy may guide adjuvant treatment decisions for TNBC and human epidermal growth factor receptor 2 (HER2)-positive BC.(36, 37) The CREATE-X and KATHERINE trials enrolled few older individuals but did not show any new safety concerns. Therefore, fit older patients should be considered for such approaches in case of residual disease.

Neoadjuvant endocrine therapy (ET) is associated with lower toxicity, reasonable response rates, and similar breast-conservation rates as neoadjuvant chemotherapy, but survival data are not available. This approach may be useful in older patients not deemed suitable for upfront surgery pending preoperative assessments. Aromatase inhibitors (AI) are recommended over tamoxifen due to improved clinical and radiological response and breast conservation rates.(38) A course of 4-6 months should be considered.

Surgery

While surgery remains the standard treatment in most older patients with early disease, there is a risk of over-treatment with competing mortality risks warranting the use of GA and survival estimates before proceeding with it.(39) However, BC surgery is generally safe, whereas endocrine therapy may cause side effects potentially impacting QoL.(22)

Surgery or not

Two systematic reviews demonstrate a local control and survival benefit with surgery over primary endocrine therapy (PET) in patients with a life expectancy ≥ 5 years.(40, 41) However, in a large cohort study, no BC-specific survival differences were seen between surgery and PET in strong hormone receptor (HR)-positive disease.(42) When PET involves aromatase inhibitors (AIs), the median time to progression is approximately five years.(42) The benefit of PET versus upfront surgery is expected to be more pronounced with a life expectancy of less than 5 years.

Ductal carcinoma in-situ (DCIS)

Opportunistic screening exposes older patients to potential over-diagnosis and over-treatment of DCIS. Ongoing non-intervention trials will define the role of ‘watch and wait’ approaches. Meanwhile, fit patients with high-grade DCIS and no multimorbidities should undergo surgery. In low- and intermediate-grade DCIS, surgery and/or postoperative radiotherapy may be spared based on life expectancy and competing risks.(43)

Surgery to the axilla

Less invasive approaches to the axilla in case of cN0 disease are particularly relevant for older adults. Axillary clearance does not produce any survival benefit, and in older patients regional recurrences without axillary surgery remains rare.(44) Therefore, in older adults, sentinel node biopsy (SNB) should be ‘standard’ for clinically/radiologically node-negative axillae. In most cases further axillary surgery can be avoided if only 1-2 sentinel nodes are involved(45) or replaced by radiotherapy.(46) As even SNB is associated with side effects and likely does not improve prognosis by itself, omission of axillary staging by SNB may be appropriate for frail individuals with low-volume, luminal A-like tumours.

Oncoplastic and reconstructive surgery

Oncoplastic and reconstructive surgery are offered less frequently to older patients.(47) Some older patients may decline such approaches more frequently compared with their younger counterparts, but their personal preferences should be balanced with risks. Oncoplastic and reconstructive procedures may be reasonable alternatives to simple mastectomy or breast conservation.(47) The pros and cons of complex versus simpler procedures should be carefully assessed and discussed with patients.

Radiotherapy

Radiotherapy after breast conserving surgery

Postoperative whole breast radiotherapy (WBRT) halves the risk of first recurrence and remains standard-of-care for most older patients following breast conserving surgery (BCS).(48) However, the absolute benefit in older patients with low-grade, HR-positive disease is modest. Omission of radiation therapy (RT) remains controversial. The CALGB 9343 trial

showed a loco-regional recurrence rate without RT of 10%, versus 2% with RT after 12 years of follow-up in women aged over 70, with no detrimental impact on OS, and these relapses could be corrected successfully by second and deferred surgery.(49) The PRIME II trial showed a lower risk of ipsilateral breast tumour recurrence (IBTR) at 5 years for those receiving WBRT.(50) Both studies suggest omitting radiotherapy in low-risk patients may be reasonable and the results of the PRIMETIME study are awaited. Recommendations regarding radiotherapy omission in low-risk patients from the 2017 NCCN and National Institute for Care and Clinical Excellence guidelines are presented in Table 3.

Tumour bed boost

In the EORTC boost/no boost trial,(51) the relative risk reduction was not statistically significant for patients aged over 60 years. Therefore, a boost is advised in this age group only in case of a higher risk of recurrence.

Partial breast irradiation

No trials of partial breast irradiation (PBI) focused specifically on older patients. The GEC-ESTRO trial of multicatheter brachytherapy versus WBRT suggested that PBI is not inferior to WBRT.(52) The UK IMPORT-LOW trial showed that partial breast and reduced dose EBRT is non-inferior to standard WBRT, with equivalent or fewer side effects.(53) The UK consensus recommends PBI to women aged ≥ 50 years or with grade 1-2, pN0, HR-positive, HER2-negative, tumours ≤ 30 mm and with radial margins ≥ 1 mm.(54)

Regional nodal irradiation

Three randomised controlled trials show the benefit of regional nodal irradiation (RNI) in high-risk early BC,(46, 55, 56) however none specifically focused on older patients. RNI is indicated in patients with 4 or more positive nodes, but it is unclear which group of patients with 1-3 positive nodes benefit from it.(57)

Postmastectomy radiotherapy

Evidence supporting the role of postmastectomy radiotherapy (PMRT) in older women is lacking and recommendations are extrapolated from analyses conducted in younger patients. PMRT is standard of care in patients with ≥ 4 positive nodes, whilst the role of PMRT in patients with 1-3 positive nodes remains controversial. An EBCTCG meta-analysis showed PMRT reduced 20-year BC-mortality by 7.9% for patients with 1-3 positive lymph nodes and

by 9.3% for patients with ≥ 4 positive lymph nodes.(48) Therefore, some argue that PMRT should be standard for all node-positive patients, while others question its role in the context of current treatment approaches. Specific guidelines are available.(9, 58, 59) The BIG 2-04 MRC SUPREMO trial evaluating PMRT in patients with 1-3 positive nodes or pN0 with LVI/grade 3 with no upper age limit remains in follow-up phase.(60) While NICE and NCCN guidelines suggest that decision-making should be driven by nodal disease burden, (58, 61) the ASCO-ASTRO-SSO recommendations highlight the relevance of age, life expectancy, multimorbidities, tumour burden and biology.(59)

Dose fractionation schedules after breast conserving surgery or mastectomy

Hypofractionated schedules are recommended for older as in younger patients as per the FAST FORWARD study results.(62)

Adjuvant systemic therapy

Adjuvant chemotherapy in older adults with HER2-negative disease

BC subtype and stage are key in informing adjuvant chemotherapy decisions. Prospective trials(63) and large retrospective cohorts(64, 65) confirm the potential large benefit of adjuvant chemotherapy on BC-specific survival or overall survival mostly in ER-negative disease, irrespective of nodal status. A recent retrospective study showed OS benefit in patients aged ≥ 70 years with node-positive, ER-positive, HER2-negative BC, also with comorbidities,(66) despite selection bias remains a significant limitation. For luminal disease, genomic tools may identify those who might benefit from chemotherapy. However, most gene expression assay validation studies excluded older patients and do not address competing risks. OncotypeDx® remains the most frequently studied tool in this age group. Its prognostic accuracy is not influenced by age, but disappointingly a high RS does not predict adjuvant chemotherapy benefit in older patients.(67) Therefore, integrating general health status with gene prognostic models is essential. Nonetheless, although results should be interpreted cautiously, this should not disqualify older patients from such tests. The ASTER 70s study will clarify the role of tumour genomic data in older BC patients.

Online prediction tools are affordable but have substantial limitations in older patients.(68) NHS PREDICT is accurate in older patients only when predicting outcomes at 5 years (but not

at 10 years) and is not reliable in the presence of multimorbidities and over 80 years.(69) Additionally, it estimates survival but not the risk of recurrence. The Age Gap Decision Tool is promising in comparing local treatment with or without chemotherapy but requires prospective validation (<https://agegap.shef.ac.uk/>).

Chemotherapy regimen choice

Although no evidence supports differential use of adjuvant chemotherapy, older adults may experience more frequent adverse events including death.(70) Benefits of adjuvant combination chemotherapy are maintained at least up until age 70, although biased by chemotherapy duration(71) and limited to HR-negative and/or node-positive disease.(65)

Modified regimens should not be utilised in older patients (Table 4). The CALGB 49907 trial showed significantly worse survival with capecitabine versus standard regimens (four cycles of doxorubicin/cyclophosphamide [AC] or six cycles of cyclophosphamide/methotrexate/fluorouracil [CMF]) in older women, with a high interaction of ER status and competing risks diluting overall survival benefits with longer follow-up.(63) The ELDA trial demonstrated worse QoL with docetaxel versus CMF and no survival benefit.(72)

Older adults were excluded or highly selected in trials of sequential anthracycline and taxane-based regimens, which should be considered only in fit patients with large, node-positive, triple-negative tumours. Dose-dense regimens should not be utilised based on the increased toxicity risk and the lack of efficacy data in older persons. In many older patients, four cycles of docetaxel/cyclophosphamide (TC) may be appropriate, which is superior to AC and more tolerable.(73) Weekly paclitaxel may be considered for high-risk patients unfit for polychemotherapy. Table 4 illustrates common chemotherapy regimens that may be considered.

Safety of adjuvant chemotherapy in older adults

Older patients have higher risk of chemotherapy toxicity and mortality.(74) Risks include haematological toxicity, anthracycline-associated cardiotoxicity (occurring in up to 38%), taxane-related neurotoxicity, falls, decreased QoL, and hospitalisations. However, functional

decline and impaired QoL may be temporary.(75) Long-term consequences include musculoskeletal events, acute myeloid leukaemia/myelodysplastic syndrome, cognitive decline, and impaired function. Chemotherapy duration (double for sequential versus single-agent regimens) should be limited, with a 3-month threshold for increased serious side effects.(20)

Anti-HER2 treatment in adjuvant setting

Although adjuvant trastuzumab is beneficial regardless of age,(76, 77) anti-HER2 (neo)adjuvant strategies remain poorly investigated in patients ≥ 65 years. Pertuzumab may be considered for high-risk individuals,(37) but diarrhoea may be debilitating in older adults, as with adjuvant neratinib (Table 4).

SIOG recommends adjuvant chemotherapy along with one year of trastuzumab as a standard approach in older patients with normal cardiac function and early-stage HER2-positive BC larger than 0.5 cm, and consideration of pertuzumab only in selected high-risk and fit patients (Table 4).(78) The preferred chemotherapy backbone includes four cycles of TC or weekly paclitaxel. Although evidence is scarce, omission of chemotherapy and utilisation of single-agent trastuzumab (plus endocrine therapy if indicated),(79) may be appropriate in vulnerable and frail patients.(78) A shorter course of adjuvant anti-HER2 therapy may also be considered for older patients with small, node-negative disease or cardiac problems.

Safety of anti-HER2 therapy in older persons

Age correlates with higher cardiac toxicity rates on trastuzumab,(80) with 15-40% of patients requiring early discontinuation especially ≥ 80 years of age and with multimorbidities,(81) likely predominantly due to chemotherapy-related adverse events. However, up to one third of cardiac events occur within two years of treatment completion, which may be more specifically related to trastuzumab.

Role of adjuvant endocrine treatment

All postmenopausal women suitable for ET should be offered endocrine therapy regardless of age. However, ET may be omitted in the absence of any documented impact on mortality in patients with very low-risk disease and/or short life expectancy.(82)

Choice of agent

Selection of agents should take into account multimorbidities and recurrence risk. AIs result in slightly better reduction in recurrence and BC-specific mortality compared to tamoxifen, and are preferable upfront especially in high-risk patients.(83) Following a few years of AIs, switching to tamoxifen is similarly effective to their continuation. Musculoskeletal side effects may impair adherence to AIs Long-term problems may include osteoporosis, cardiovascular risk, diabetes, hypercholesterolemia and cognitive impairment. Conversely, AIs are associated with a lower risk of venous thrombosis, endometrial cancer and fatty liver disease compared to tamoxifen. Good compliance should drive treatment decisions.

Duration of therapy

Letrozole improves survival outcomes versus placebo among patients who receive an initial five-year course of tamoxifen. After five initial years of AIs, data are less clear: a recurrence-free survival (RFS) benefit is not confirmed in all studies although bone-related adverse events are more frequent. The more modest impact on RFS and the impact on bone health is confirmed by large meta-analyses. Therefore, the current standard of care should include five years of ET, and extended therapy may be offered to fit, healthy older women with high-risk disease who tolerated the first five years.(84) In frail patients, recommendations should be guided by the individual circumstances.

Role of adjuvant bone modifying agents

Adjuvant systemic therapies for BC are associated with an increased risk of bone loss. Therefore, a baseline assessment of bone mineral density (BMD) in older patients suitable for adjuvant endocrine therapy is mandatory, followed by calcium and vitamin D supplementation and use of bisphosphonates to preserve bone mass while on AIs. Also, adjuvant bisphosphonates also improve survival outcomes in patients with early-stage disease.(85) An

EBCTCG meta-analysis documented a 2-3% benefit in BC-mortality limited to postmenopausal women receiving bisphosphonates.(86)

Zoledronate or clodronate should be offered regardless of age to postmenopausal women with moderate- to high-risk BC according to international consensus. Evidence is insufficient for alendronate and risedronate. Bisphosphonate use should take into account the minor improvement in long-term survival and their potential side effects, including electrolyte disturbances (mostly hypocalcemia), atypical fractures and osteonecrosis of the jaw,(87, 88) multimorbidities, renal function, fitness and patient preferences. The role of denosumab is controversial and should not be considered in the adjuvant setting for older patients to reduce mortality. The ABCSG-18 study showed improved DFS and bone fracture rate in patients on adjuvant denosumab(89) but the subsequent D-CARE study failed to detect any benefit in bone metastasis-free survival or DFS.(90) Additionally, a rebound effect with more vertebral fractures occurring upon its discontinuation has been demonstrated.

Systemic treatment for metastatic disease

Different treatment schedules, dose reductions or stepwise dose-escalation before reaching standard recommended dose might be required in older patients(91) and reduce the risk of adverse outcomes.

Chemotherapy

Chemotherapy should be considered in suitable older patients with HR-negative disease, HR-positive disease resistant to ET or with rapidly progressive disease and/or extensive visceral involvement and based on GA and patient preferences. The increased toxicity risk in this age group mandates particular attention to minimising side effects.(8) Single-agent regimens are preferred over polychemotherapy(6) and chemotherapy toxicity prediction tools may also be useful. Preference should be given to agents studied in older populations. Nab-paclitaxel is associated with very few allergic reactions, does not require steroids and is safe and effective in patients over 65.(92) Following anthracyclines or taxanes, eribulin is also appropriate, with similar efficacy and toxicity regardless of age and no impact on GA parameters nor QoL.(93)

HER2-positive metastatic breast cancer

Older patients with HER2-positive metastatic BC and adequate cardiac function should receive HER2-directed therapy based on fitness.(78) Although docetaxel or paclitaxel in combination with trastuzumab and pertuzumab are recommended in fit patients, taxanes may cause severe toxicities. In older patients not suitable for taxanes, capecitabine or vinorelbine may be considered. The EORTC 75111-10114 study(94) enrolling older patients evaluated trastuzumab and pertuzumab with or without metronomic oral cyclophosphamide. Vinorelbine along with dual anti-HER2 blockade may also be considered.

ET with trastuzumab plus pertuzumab or lapatinib is a reasonable alternative for patients with ER-positive disease, despite diarrhoea may be an issue requiring close monitoring. T-DM1 is recommended in later therapy lines in fit older patients, but further research in frail patients is warranted.

Targeted agents in luminal tumours

Efficacy of cyclin-dependent kinases 4/6 (CDK4/6) inhibition is age-independent in the subgroup and pooled analyses of the landmark studies of palbociclib, ribociclib and abemaciclib,(95-98) with no age-related changes in pharmacokinetics. Nevertheless, patients ≥ 75 years experience higher rates of toxicity and dose modifications.(98) While ET alone is still reasonable in selected cases, CDK4/6 inhibitors are a suitable treatment in older patients.(99)

Everolimus should be used with caution in older patients in view of its safety profile. A subgroup analysis of the BOLERO-2 study revealed a higher rate of discontinuations in patients ≥ 70 years and more on-treatment deaths.(100) 26% of patients enrolled in the expanded-access BALLET trial were aged ≥ 70 , which similarly reported more frequent AE-related dose discontinuations, reductions and interruptions.

Supportive care

Supportive care is important as cancer and its treatment can seriously harm and lead to various degrees of decompensation of older patients. For detailed guidance, the reader can also consult

the ESMO, MASCC and SIOG websites (<https://www.esmo.org/>; <https://www.mascc.org/>; <https://www.siog.org/>).

Digestive symptoms

Nausea and vomiting can be treatment-related or have alternative aetiologies. In older individuals, diagnosis may be challenging as clinical signs may be absent or atypical. Guidelines for prevention of chemotherapy and radiation therapy-induced nausea and vomiting should be followed. General management guidelines for diarrhoea, constipation and stomatitis are available.

Malnutrition

More than 30% of older patients experience severe malnutrition in the hospital and nursing home settings. Malnutrition can lead to osteopenia/osteoporosis, sarcopenia, immunological deficiencies and iron, vitamin B12 or folate-related anaemia, and predicts outcomes at three years. This may be improved by timely intervention.

Depression

Depression in older cancer patients is often under-recognised and untreated but can be successfully managed with psychological support, and antidepressants when indicated. Drug interactions should be considered, such as those between selective serotonin-reuptake inhibitors and tamoxifen.

Pain control

Pain can be related to or complicated by multimorbidities such as arthritis or osteoporotic fractures. Older patients are generally more susceptible to changes in drug doses, side effects, and drug interactions. Particular attention should be paid to potential side effects of nonsteroidal anti-inflammatory drugs (renal function, gastric ulcers). Guidelines are available, with the above caveats.

Febrile neutropenia prevention and treatment

Guidelines on the primary prophylactic use of white blood cell growth factors acknowledge the increased risk of myelosuppression in individuals aged >65. In the general population, the febrile neutropenia risk threshold of $\geq 20\%$ is for consideration of primary prophylaxis, but for older persons, a lower threshold may be used, e.g. $>10\%$, which is reached in older persons when using standard myelosuppressive regimens as anthracyclines or TC.

Conclusions

The management of BC in older adults should involve routine use of GA tools and close interaction with members of the multidisciplinary team due to the intrinsic heterogeneity of this population. In the context of the limited applicability of the evidence generated in younger and/or more fit individuals, patient preferences, life expectancy, predicted survival benefits and impact on toxicity and QoL should be carefully considered in decision-making.

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