Clinical Interventions in Aging

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REVIEW

Adjuvant Chemotherapy for Breast Cancer in Older Adult Patients

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Abstract: Decision-making regarding adjuvant chemotherapy for older adults with breast cancer is a challenge because older adult patients often have poor physical health, frailty, and age-related comorbidities, which can compromise treatment outcome. Due to these considerations, doctors tend to use less chemotherapy for breast cancer in older adults. However, older patients in good general health could still benefit from chemotherapy. Careful benefit-risk assessment is essential to provide best care for each older adult patient. Due to a rapidly aging population, breast cancer in older adults is becoming a serious public health issue in China. In this mini review, we discuss the need, means, and tools to assess the benefits and risks of adjuvant chemotherapy in older adults with breast cancer. The contents of this review may drive decision-making with regard to the use and selection of adjuvant chemotherapy for older adult patients in China who are fit for the treatment.

Keywords: breast cancer, older adult patients, chemotherapy, assessment

Introduction

Breast cancer is the most common female cancer and the leading cause of cancer mortality in women worldwide.[1] According to data from the National Cancer Institute (NCI), approximately 13% of the women born in America will develop breast cancer in their lifetime. Breast cancer incidence and related-deaths increase with age, with women aged 70 and older accounting for about 30% of all breast cancer cases and half of all breast cancer-related deaths.[2] China has a rapidly aging population, with 190 million people (13.5% of its population) aged 65 and older.[3] As such, breast cancer in older adults is becoming a significant public health problem in China.

Breast cancer treatment is highly individualized, and prognosis is being improved by tailoring treatment to the patient's genetic makeup, as well as to the size and range of the tumor. Adjuvant chemotherapy can be given after surgery to reduce recurrence or to palliatively treat unresectable metastatic tumors. Because older adult patients often have poor physical health, age-related comorbidities, or competing causes of mortality, they may have an increased risk of chemotherapy intolerance and/or poorer treatment response. Due to these considerations, doctors tend to avoid using chemotherapy in older adults with breast cancer. However, clinical data indicated that similar to younger women, older adults in good physical health can benefit from chemotherapy.[4] Thus, careful benefit-risk assessment is essential to provide the best care for each older adult patient. Based on this, the EUSOMA (European Society of Breast Cancer Specialists) and SIOG (The International Society of Geriatric Oncology) guidelines for the management of breast cancer in older adults were updated in 2021 to include chemotherapy toxicity prediction and treatment recommendations.[5] In 2018, ASCO (American Society of Clinical Oncology) published guidelines for practical assessment and management of vulnerabilities in geriatric breast cancer patients receiving chemotherapy.[6]

In this mini review, we discuss the need, means, and tools to evaluate the benefits and risks of adjuvant chemotherapy in older adults with breast cancer. This may help drive decision-making with regard to the use and selection of adjuvant chemotherapy for older adult patients in China and improve their clinical outcome.

Received: 22 March 2024
Accepted: 15 June 2024
Published: 16 July 2024

Immunohistochemical (IHC) Characteristics of Breast Cancer in Older Adults

Breast cancer is commonly categorized into subtypes including luminal A, luminal B, human epidermal growth factor receptor (HER2)-positive, and triple-negative (TNBC), according to the IHC expression of the estrogen receptor (ER), progesterone receptor (PR), and HER2. Luminal A breast cancer (ER+/PR+/HER2-) often responds well to hormone therapy and occasionally to chemotherapy. Luminal B breast cancer (ER+/HER2+) is likely sensitive to chemotherapy, and it also may respond to hormone therapy and HER2-targeted therapy. HER2+ breast cancer (ER-/PR-/HER2+) is often sensitive to chemotherapy and HER2-targeted therapy. Without hormone receptor expression, TNBC does not benefit from hormone therapy or HER2-targeted therapy, leaving chemotherapy and immunotherapy as the primary treatment options for this breast cancer subtype.

Compared with younger patients, older adult patients are somewhat more likely to have cancers with favorable biologic characteristics such as normal p53, slow proliferation, and being node-negative, hormone receptor-positive, and HER2-negative.[7–9] Nonetheless, 15%-18% of older adult patients still develop TNBC, an aggressive subtype of breast cancer.[10] In a 2016 study on 1362 breast cancer patients aged 65 and older, the percentages of luminal A, luminal B, HER2-positive, and TNBC subtypes were found to be 75%, 3%, 7.6%, and 7.1%, respectively.[11]

Genetic Characteristics of Breast Cancer in Older Adults

Age-related genetic and epigenetic alterations may be linked to an increased risk of breast cancer in older adults.[12] Analyses on The Cancer Genome Atlas (TCGA) dataset found that breast cancer patients aged 70 and older had more somatic mutations and copy number variations (CNVs) than those aged 45 and younger.[13] Older patients had 44 somatic mutations on average while younger patients had 31. The most common somatic mutations were PIK3CA and TP53 in both age groups, accounting for 50–60% of all mutations. Of note, 11 somatic mutations were found to be independently associated with age. Ten of the 11 somatic mutations were associated with older age, and only one (GATA3) was associated with younger age (15.2% in younger patients versus 9% in older patients). Of the somatic mutations associated with older age, KMT2D is of particular significance since this gene has been found to regulate tumor cell proliferation and migration.[14] Another significant finding was the higher incidence rate of FOXA1 mutations in older patients. FOXA1 is required for ER-α-mediated proliferation and survival of luminal tumors.[15] KMT2D and FOXA1 each accounted for only 0.8% of all mutations in younger patients but 5.8% in older patients.[13] The higher incidence rate of KMT2D and FOXA1 mutations in older patients may be linked to the increased breast cancer risk in older adults.

Prognosis of Older Adult Breast Cancer Patients

Compared with younger breast cancer patients, older patients are more likely to have tumors of lower grade, smaller size, higher ER and/or RP expression, and lower lymph node positivity.[16,17] A retrospective survival analysis of 52,509 breast cancer patients in America found that older patients had higher disease-free survival and overall survival than younger patients.[18] In the UK, older patients have lower rates of surgery for operable breast cancer than younger patients.[19] For older patients (aged 70 and older) with ER-positive disease, surgery had a positive impact on 5-year disease-specific survival (89.9% with surgery vs 69.4% without surgery), although for patients with severe frailty and comorbidity, surgery provided lessened survival benefit over primary endocrine therapy.[20] Thus, when considering surgery as a treatment option for operable breast cancer in older patients, decision makers should evaluate not only the TNM staging and characteristics but also the individual patient's general physical health and cognitive function, comorbidity, and life expectancy.[21,22]

In a SEER (Surveillance, Epidemiology, and End Results) population-based study, older adults with breast cancer (aged 70 and older) exhibited a negative attitude toward radiotherapy and chemotherapy.[23] A vast majority of the entire population (75,525) underwent surgery, and approximately 50% of the patients received radiation therapy. Only a small portion (15.9%) received chemotherapy. Compared with patients who did not undergo radiation or chemotherapy, those who received radiation or chemotherapy had reduced risk of disease-specific death.[23] Thus, for older breast cancer patients without major comorbidity, personalized adjuvant chemotherapy should provide additional survival benefit.

Adjuvant Chemotherapy for Older Adult Breast Cancer Patients

According to the 2021 EUSOMA and SIOG recommendations with regard to the management of older adults with breast cancer,[5] decision-making on adjuvant chemotherapy should not be driven by age alone but should involve consideration of the molecular subtype and clinicopathological characteristics of the disease, as well as patient geriatric scores and life expectancy. Older patients with hormone receptor-negative disease may benefit the most from adjuvant chemotherapy regardless of nodal status. Standard regimens are four cycles of docetaxel plus cyclophosphamide or doxorubicin plus cyclophosphamide. Patients unfit for polychemotherapy (CMF or an anthracycline-containing regimen) may receive weekly paclitaxel for 12 weeks. Taxanes are associated with greater toxicity in older patients than younger patients. Thus, only fit patients with high-risk disease should be considered for a sequential combination of anthracyclines and taxanes, and dose-dense regimens should be avoided. Of particular note, chemotherapy beyond 3 months may increase the risk of serious side-effects.[24]

Tools for Survival Estimate in Older Adults

Chemotherapy-associated risks may outweigh the benefits in cancer patients with limited life expectancy. According to the 2021 EUSOMA and SIOG recommendations,[5] older breast cancer patients who are expected to live more than 4 years may benefit from disease-specific therapy. Therefore, treatment decision-making for older patients should involve consideration of estimated survival time. Tools for survival estimates include Lee index,[25] Carey index,[26] Gagne index,[27] Schonberg index,[28] and the combined Lee-Schonberg index (https://eprognosis.ucsf.edu/leeschonberg.php). The combined Lee-Schonberg index estimates survival time of older patients based on age, gender, physical activities, nutritional level, history of hospitalization, and cognition and emotion status. This index can predict all course 4–14 year mortality for adults aged 50 and older with >70% accuracy and, therefore, its results can be used to aid clinical decision-making regarding treatment plans for older breast cancer patients.

Risk-Benefit Assessment of Chemotherapy for Older Adult Breast Cancer Patients

When treating older adults with breast cancer, treatment goals should be clearly defined to guide shared decision-making. Early-stage disease can be cured, but for advanced disease, the goal of treatment is to control symptoms, improve or sustain quality of life, and prolong survival. Careful assessment of risks and benefits is critical for identifying older patients who can potentially benefit from chemotherapy. The methods for risk-benefit assessment are presented in Table 1.

Prediction of Toxicity in Older Adult Breast Cancer Patients Receiving Chemotherapy

The Cancer and Aging Research Group (CARG) (https://www.mycarg.org/) provides a chemotherapy toxicity calculator that can predict the risk of grade 3–5 toxicity in cancer patients receiving chemotherapy based on age, gender, cancer type, geriatric assessment variables, and chemotherapy regimen (Table 2). The CARG model has successfully predicted chemotherapy tolerability in older patients with early-stage[29] or metastatic[30,31] breast cancer. In addition, the Chemotherapy Risk Assessment Scale for High-Age Patient (CRASH) captures 24 variables to generate a predictive

Table 1 Risk-Benefit Assessment for Chemotherapy in Older Adult Breast Cancer Patients

	Data Source	Predictive Results	Clinical Endpoints	Feasibility in Older Adult Patients
Adjuvant! Online	SEER database	Benefits of chemotherapy and endocrine therapy	Disease-specific deaths; Non-disease-specific deaths	Overestimation of 10-year overall survival and disease-free survival
PREDICT	UK National Cancer Registration database	Benefits of chemotherapy, endocrine therapy, and targeted therapy	Disease-specific deaths	Accurate estimation of 5-year overall survival; Overestimation of 10-year overall survival
21-Gene expression analysis	TAILORx trial	Benefits of chemotherapy in hormone receptor-positive, HER2-negative, node-negative disease	Invasive disease-free survival; Distant recurrence-free interval	Patients over 75 excluded; only 5% of patients were aged 70 or older

Table 2 Models for Predicting Toxicity in Older Adult Breast Cancer Patients Receiving Chemotherapy

	CARG	CRASH
General health variables	Age	Age; BMI; Diastolic blood pressure; ECOG score; Self-rated health
Disease-specific variables	Cancer type	Cancer type, stage, and bone marrow invasion
Treatment-related variables	Chemotherapy regimen and dose	Treatment type (surgery, radiation therapy, chemotherapy, etc.)
Hematologic and biochemical variables	Hemoglobin; Creatinine clearance	WBC; Platelets; Hemoglobin; Aspartate aminotransferase; Lactate dehydrogenase; Albumin
Geriatric assessment variables	Hearing loss; Number of falls in the past 6 months; Ability to take medications; Self-care ability; Ability to walk one block; Social activity level	Nutritional status; Independent living skills; Cognitive impairment; CIRS-G score, etc.

score for chemotherapy toxicity in older adults with breast cancer (Table 2). In a prospective, multicentric study on 518 older patients with a hematologic malignancy or solid tumors starting chemotherapy, the CRASH model successfully predicted grade 4 hematologic or grade 3/4 nonhematologic toxicity.[32] Minor modifications of the CRASH model may be necessary to allow accurate prediction of chemotherapy toxicity in older adult patients with a specific cancer type. Although the CARG and CRASH models are not fully validated for toxicity prediction in older adults with breast cancer, the CARG and CRASH scores can be used to aid decision-making concerning the use and selection of chemotherapy in older patients, secondary to clinical judgment and patient preferences.

Summary

When considering chemotherapy for older adults with breast cancer, decision-making should not be based on age alone but should involve comprehensive geriatric assessments on physical, cognitive, and mental health plus consideration of estimated life expectancy and patient personal preferences. The use and selection of chemotherapy should follow relevant recommendations from EUSOMA, SIOG, and ASCO, and should be driven by careful risk-benefit assessment in each older adult patient.

Outlook

Multiple clinical trials are evaluating the efficacy and safety of novel targeted therapy and immunotherapy for breast cancer, such as endocrine therapy plus CDK4/6 or mTOR inhibitors for ER+/HER2- advanced breast cancer,[33,34] trastuzumab plus a tyrosine kinase inhibitor for HER2+ breast cancer,[35,36] PARP inhibitor for BRCA1- or BRCA2-mutated breast cancer,[37] and immune check point inhibitors for early-stage and metastatic breast cancer.[38] The monarchE trial evaluated abemaciclib in the adjuvant setting for patients with high-risk early-stage breast cancer (ie, ≥4 pathologically positive axillary nodes or 1–3 positive nodes and at least one of the following: tumor dimension ≥5 cm, G3, or Ki67 ≥20%).[39] The trial found that the addition of abemaciclib significantly improved the 2-year invasive disease-free survival. These new therapeutic regimens are supported by current clinical data and may significantly expand treatment options for breast cancer. With careful risk-benefit assessment in older adults, these new treatments may also reshape the landscape of adjuvant chemotherapy for older adult breast cancer patients.

Funding

Tianjin Medical Key Discipline (Specialty) Construction Project (TJYXZDXK-058B), Tianjin Municipal Science and Technology Project (21JCZDJC00360) Tianjin Health Research Project (TJWJ2022XK024).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Cancer Research UK. Breast cancer statistics (2021). Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer. Accessed June 20, 2024.
2. Kubista E. Das Mammakarzinom: Zahlen und Fakten [Breast cancer: figures and facts]. *Wien Med Wochenschr*. 2001;151(21–23):548–551. German.
3. Communiqué of the Seventh National Population Census. *National Bureau of Statistics of China 2020*; 2020.
4. Muss HB, Woolf S, Berry D, et al. Adjuvant chemotherapy in older and younger women with lymph node-positive breast cancer. *JAMA*. 2005;293 (9):1073–1081.
5. Biganzoli L, Battisti NML, Wildiers H, et al. 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). *Lancet Oncol*. 2021;22(7):e327–e340.
6. Mohile SG, Dale W, Somerfield MR, et al. Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology. *J Clin Oncol*. 2018;36(22):2326–2347.
7. Diab SG, Elledge RM, Clark GM. Tumor characteristics and clinical outcome of elderly women with breast cancer. *J Natl Cancer Inst*. 2000;92 (7):550–556.
8. Wildiers H, Kunkler I, Biganzoli L, et al. Management of breast cancer in elderly individuals: recommendations of the International Society of Geriatric Oncology. *Lancet Oncol*. 2007;8(12):1101–1115.
9. Biganzoli L, Wildiers H, Oakman C, et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). *Lancet Oncol*. 2012;13(4):e148–160.
10. Aapro M, Wildiers H. Triple-negative breast cancer in the older population. *Ann Oncol*. 2012;23(Suppl 6):vi52–55.
11. Engels CC, Kiderlen M, Bastiaannet E, et al. The clinical prognostic value of molecular intrinsic tumor subtypes in older breast cancer patients: a FOCUS study analysis. *Mol Oncol*. 2016;10(4):594–600.
12. Ueno T, Emi M, Sato H, et al. Genome-wide copy number analysis in primary breast cancer. *Expert Opin Ther Targets*. 2012;16 Suppl 1:S31–35.
13. Azim HA, Nguyen B, Brohee S, Zoppoli G, Sotiriou C. Genomic aberrations in young and elderly breast cancer patients. *BMC Med*. 2015;13:266.
14. Guo C, Chen LH, Huang Y, et al. KMT2D maintains neoplastic cell proliferation and global histone H3 lysine 4 monomethylation. *Oncotarget*. 2013;4(11):2144–2153.
15. Carroll JS, Liu XS, Brodsky AS, et al. Chromosome-wide mapping of estrogen receptor binding reveals long-range regulation requiring the forkhead protein FoxA1. *Cell*. 2005;122(1):33–43.
16. Azim HA, Partridge AH. Biology of breast cancer in young women. *Breast Cancer Res*. 2014;16(4):427.
17. Feng F, Wei Y, Zheng K, et al. Comparison of epidemiological features, clinicopathological features, and treatments between premenopausal and postmenopausal female breast cancer patients in western China: a retrospective multicenter study of 15,389 female patients. *Cancer Med*. 2018;7 (6):2753–2763.
18. Nasrazadani A, Marti JLG, Kip KE, et al. Breast cancer mortality as a function of age. *Aging*. 2022;14(3):1186–1199.
19. Lavelle K, Downing A, Thomas J, Lawrence G, Forman D, Oliver SE. Are lower rates of surgery amongst older women with breast cancer in the UK explained by co-morbidity? *Br J Cancer*. 2012;107(7):1175–1180.
20. Ward SE, Richards PD, Morgan JL, et al. Omission of surgery in older women with early breast cancer has an adverse impact on breast cancer-specific survival. *Br J Surg*. 2018;105(11):1454–1463.
21. Morgan JL, Walters SJ, Collins K, et al. What influences healthcare professionals' treatment preferences for older women with operable breast cancer? An application of the discrete choice experiment. *Eur J Surg Oncol*. 2017;43(7):1282–1287.
22. Wyld L, Reed MWR, Collins K, et al. Bridging the age gap in breast cancer: cluster randomized trial of two decision support interventions for older women with operable breast cancer on quality of life, survival, decision quality, and treatment choices. *Br J Surg*. 2021;108(5):499–510.
23. Yang R, Wu Y, Qi Y, et al. A nomogram for predicting breast cancer specific survival in elderly patients with breast cancer: a SEER population-based analysis. *BMC Geriatr*. 2023;23(1):594.
24. Hurria A, Magnuson A, Gross CP, et al. Development and validation of a chemotherapy toxicity (Chemo Tox) risk score for older patients (Pts) with breast cancer (BC) receiving adjuvant/neoadjuvant treatment (Adjuvant Tx): a R01 and BCRF funded prospective multicenter study. *Cancer Res*. 2019;79(4).
25. Lee SJ, Lindquist K, Segal MR, Covinsky KE. Development and validation of a prognostic index for 4-year mortality in older adults. *JAMA*. 2006;295(7):801–808.
26. Carey EC, Covinsky KE, Lui LY, Eng C, Sands LP, Walter LC. Prediction of mortality in community-living frail elderly people with long-term care needs. *J Am Geriatr Soc*. 2008;56(1):68–75.
27. Gagne JJ, Glynn RJ, Avorn J, Levin R, Schneeweiss S. A combined comorbidity score predicted mortality in elderly patients better than existing scores. *J Clin Epidemiol*. 2011;64(7):749–759.
28. Schonberg MA, Davis RB, McCarthy EP, Marcantonio ER. External validation of an index to predict up to 9-year mortality of community-dwelling adults aged 65 and older. *J Am Geriatr Soc*. 2011;59(8):1444–1451.
29. Magnuson A, Sedrak MS, Gross CP, et al. Development and Validation of a Risk Tool for Predicting Severe Toxicity in Older Adults Receiving Chemotherapy for Early-Stage Breast Cancer. *J Clin Oncol*. 2021;39(6):608–618.
30. Hurria A, Soto-Perez-de-Celis E, Blanchard S, et al. A Phase II Trial of Older Adults With Metastatic Breast Cancer Receiving nab-Paclitaxel: melding the Fields of Geriatrics and Oncology. *Clin Breast Cancer*. 2019;19(2):89–96.
31. Yuan Y, Lee JS, Yost SE, et al. Phase II study of neratinib in older adults with HER2 amplified or HER2/3 mutated metastatic breast cancer. *J Geriatr Oncol*. 2021;12(5):752–758.
32. Extermann M, Boler I, Reich RR, et al. Predicting the risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. *Cancer*. 2012;118(13):3377–3386.
33. Xu B, Zhang Q, Zhang P, et al. Dalpiciclib or placebo plus fulvestrant in hormone receptor-positive and HER2-negative advanced breast cancer: a randomized, Phase 3 trial. *Nat Med*. 2021;27(11):1904–1909.

34. Bardia A, Hurvitz SA, DeMichele A, et al. Phase I/II Trial of Exemestane, Ribociclib, and Everolimus in Women with HR(+)/HER2(-) Advanced Breast Cancer after Progression on CDK4/6 Inhibitors (TRINITI-1). *Clin Cancer Res*. 2021;27(15):4177–4185.
35. Xu ZQ, Zhang Y, Li N, et al. Efficacy and safety of lapatinib and trastuzumab for HER2-positive breast cancer: a systematic review and meta-analysis of randomised controlled trials. *BMJ Open*. 2017;7(3).
36. Li L, Zhang D, Wu Y, Wang J, Ma F. Efficacy and safety of trastuzumab with or without a tyrosine kinase inhibitor for HER2-positive breast cancer: a systematic review and meta-analysis. *Biochim Biophys Acta Rev Cancer*. 2023;1878(6):188969.
37. Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. *N Engl J Med*. 2021;384 (25):2394–2405.
38. Cejuela M, Vethencourt A, Pernas S. Immune Checkpoint Inhibitors and Novel Immunotherapy Approaches for Breast Cancer. *Curr Oncol Rep*. 2022;24(12):1801–1819.
39. Johnston SRD, Harbeck N, Hegg R, et al. Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE). *J Clin Oncol*. 2020;38(34):3987–3998.