Chronological age or biological age: What drives the choice of adjuvant treatment in elderly breast cancer patients?

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ABSTRACT

Ma and colleagues reported in their study on 12,004 elderly patients published on Breast J. 2020, that adjuvant chemotherapy was not associated with overall survival. Given the toxicities associated with systemic treatments, caution recommendation or omission of chemotherapy may be considered in elderly patient selection especially when comorbidities are present. We agree with authors final conclusions but we want to highlight that to define the adjuvant therapy in BC elderly patients several factors need to be taken into account. One of the main issues is the lack of universal and unique guidelines to define elderly patients. In clinical practice it can be very difficult to estimate the benefit/risk ratio in elderly patients because chemotherapy-induced toxicity is worse than in younger individuals. For these reasons, beyond comorbidities, the choice of adjuvant therapy for elderly patients must also be based both on chronological and biological age. Moreover, the multidisciplinary team for the elderly patient evaluation should include both the geriatrician and the molecular biologist.

Breast cancer (BC) patients aged over 65 represent 47%, and this percentage will increase over the next 20 years (https://gis.cdc.gov/Cancer/USCS/DataViz.html). Elderly women tend to have less aggressive tumors (Luminal-A like) than other age groups.

Ma and colleagues [1] reported that elderly patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER-2) negative, node negative BC were underrepresented in prior prospective trials. In their study on 12,004 elderly patients, they demonstrated that adjuvant chemotherapy was not associated with overall survival and due to the toxicities associated with systemic treatment caution recommendation or omission of chemotherapy may be considered in elderly patient selection especially in presence of co-morbidities.

We agree with the authors with their final conclusions but we want to highlight that to define the adjuvant therapy in BC elderly patients more factors have to be taken into account.

The clinical practice for elderly patients with luminal tumor is surgery followed by adjuvant therapy (AT) in order to prevent recurrence. The adjuvant therapeutic plan consists in hormonal therapy, chemotherapy, and radiotherapy if the risk of recurrence is high.

Then, which patient age (chronological or biological) has to be considered for the choice of the adjuvant treatment (AT) in BC? In the context of cancer, defining which age needs to be taken into account to drive the choice of treatment in elderly patients is important. One of the main issues is the lack of universal guidelines to determine the biological age to define a patient as old and which other factors need to be considered to define the most appropriate treatment. Both the oncologic and geriatric risk factors affect the benefit-risk ratio of AT. The individual benefit-risk balance of AT must take into account primarily the tumor characteristic such as hormone receptors, proliferation index, Scarff Bloom Richardson score, the nodal involvement and then the patient's fitness (e.g. functional status).

To define the AT in elderly patients, chronological age may be not enough. Scarce data are present on elderly patients, due to the mismatch between those who are most likely to get cancer (people ≥65 years) and those who are often enrolled in clinical trials (people <65 years). In addition, different cut-offs to enroll elderly patients are used.

Chronological age is the amount of time that has elapsed from birth to a given date and is the main way of defining age. Biological aging occurs as a person gradually accumulates damages to various cells. Also known as physiological or functional age, biological age differs from chronological age and it considers not only the time elapsed, but also a number of different biological and physiological developmental factors [2], such as genetics, lifestyle, nutrition and comorbidities.

The patients become elderly in different ways. In fact, Bonafè and colleagues reported the importance of defining healthy aging vs unhealthy aging [3]. The latter is characterized by premature senescence, SASP (senescence-associated secretory phenotype), 'inflamm-aging' (chronic low-grade inflammation) and age-related diseases. The authors explored how to modify telomerase machinery to put the brakes on the inflamm-aging often associated with older age [3]. Several strategies have been developed to achieve telomeres elongation in humans using natural telomerase activators (TA), such as TA-65, but this compound has to be better explored in BC.

Age related changes in DNA methylation may reflect long term changes in transcriptional regulation. DNA methylation is currently the most promising molecular marker for aging monitoring and to predict life expectancy. However, the mechanisms underlying age-related changes in DNA methylation remain mostly undiscovered [4]. Several studies have been performed on epigenetic modifications to estimate "biological age" as a predictor of BC risk [4]. Kresovich and colleagues demonstrated that age acceleration is associated with invasive BC and that DNA methylation-based measure of biological age could be an important predictor of BC risk. Several epigenetic clocks have been proposed in order to define the relation between aging and outcome, but the strength of the association varies significantly across different clocks [4].

Moreover, it has been reported that tumor microenvironment (TME) plays an important role in aging [5], that is a complex process involving not only epithelial cells but also inflammatory cells [6]. Aging is characterized by inflammation [7] and inflammation, in turn, leads to aging. Studies are ongoing to investigate new therapeutic approaches capable of reversing phenotypic macrophages from alternative (protumoral) M2, which influences the development of inflammation and cancer, to classic (antitumoral) M1 [8]. The intra-tumoral stroma in BC patients increases with age [9] and can influence response to therapy. Brouwers and colleagues were the first to provide evidence that older age at diagnosis in humans is associated with a different TME in BC. SASP and evidence of autophagy appear to be important age-induced stromal features but are not usually evaluated in the clinical practice [10]. Recently, it has been shown that the tumor-stroma ratio is not an independent prognostic parameter in patients ≥70 years, in contrast to young women with BC [9]. No studies have been performed on the role of different stroma components (also in terms of gene expression profiles) in relation to AT response.

Despite the efforts on the assessment of the role of conventional and new biological markers in the context of aging, their use in the clinical practice has not been reached.

AIOM (Associazione Italiana Oncologia Medica) strongly recommends administering a polychemotherapy schedule in elderly fit patients as AT (www.aiom.it/linee-guida-aiom-neoplasie-della-mammella-2019/). In women aged 65–89 years whose tumors had a high risk of recurrence, only those in the 65–74 year age group with no or few comorbidities showed a small benefit from the addition of chemotherapy with endocrine treatment [11]. The authors concluded that genomic profiling (and use of chemotherapy) should be reserved for women <75 years with no severe comorbidities [10].

Regarding at the AT in elderly BC patients, capecitabine vs standard therapy in women aged ≥65 showed an inferior benefit as compared to conventional treatment [12].

Few studies have assessed the effect of subtype on BC-specific mortality in both young and elderly patients. A recent population-based study reported increased mortality among the elderly in all clinical BC subtypes, but not among young women [13]. Thus, further research is needed to investigate the association between BC-specific mortality and BC subtypes and to establish whether biological factors could be useful in this context [13].

In clinical practice, it can be very difficult to balance the benefits and the side effects in older patients because chemotherapy-induced toxicity is worse than in younger individuals.

Table 1

Principal factors that need to be considered to define the adjuvant treatment in elderly breast cancer patients.

Factors	Characteristics
Patient chronological Age	Old postmenopausal women (65-74 years)/ Elderly postmenopausal women (>= 75 years)
Comorbidities (i.e. Diabetes, cardiovascular diseases, neurological and cognitive diseases)	Presence of comorbid conditions/ neurological impairment (e.g. Parkinson, Alzheimer disease)/ abnormal cognitive screening (e.g. confusion and memory loss)
Anatomopathological characteristics of the tumor (tumor type and TNM)	Ductal versus lobular carcinoma, tumor size, grading, number of lymph nodes involved, lymphovascular invasion
Biological characteristic of the tumor (ER, PgR, Ki67, HER2)	Hormone receptor positive/negative, high/low proliferation, HER2 positivity/negativity
Gene expression profiling test results (e.g. Oncotype, Mammaprint, PAM50)	Low, intermediate, high recurrence score

The benefit-risk balance is complex in the clinical practice and it is even more challenging in elderly patients because chemotherapy induced toxicity is worse and the benefit are not as well established as those reported in younger patients.

Several factors such as patient age, presence of comorbidities (such as diabetes, cardiovascular diseases, neurological and cognitive diseases), anatomopathological and biological features of the tumor and the results of gene expression profiles need to be evaluated and balanced to choice the adjuvant treatment in elderly breast cancer patients (Table 1).

The few available data on the Oncotype Dx test in elderly women from retrospective analyses of recurrence scores by age are affected by selection bias. Another issue in the geriatric population is that it is under-represented in clinical trials in oncology, especially for BC.

Up to now, no new biological factors such as Telomerase or DNA methylation are used in the clinical practice to guide the physician in the choice of AT in BC patients. However, several studies have reported the potential diagnostic value of DNA methylation for early cancer detection and for cancer risk susceptibility evaluation [14–15].

More information on prognostic and predictive biological factors are needed. An indication for the use of genomic assays in early-stage BC was recently reported [16]. However, the balance between the benefit and potential adverse events must be considered in evaluating the appropriateness and sustainability of both molecular testing and treatment. The treatment of BC elderly patients requires a multidisciplinary approach and the geriatric assessment must be based on different domains: functional status, objective physical performance, falls, cognitive function, mood or depression, nutritional status, comorbidities, polypharmacy and social support [17].

The multidisciplinary group for BC elderly patients should include the geriatrician and the molecular biologist to obtain a comprehensive evaluation, to be sure of the appropriateness of the treatment considering the geriatric assessment and the last translational research results.

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2

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Roberta Maltoni: Conceptualization, Writing – original draft, Writing – review & editing. **Sara Ravaioli:** Writing – original draft, Writing – review & editing. **Giuseppe Bronte:** Writing – review & editing. **Massimiliano Mazza:** Writing – review & editing. **Claudio Cerchione:** Writing – review & editing. **Ilaria Massa:** Writing – review & editing. **William Balzi:** Writing – review & editing. **Michela Cortesi:** Writing – review & editing. **Michele Zanoni:** Writing – review & editing. **Sara Bravaccini:** Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

All authors declare no competing interests.

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