The Breast 22 (2013) 142–149

Contents lists available at SciVerse ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Aromatase inhibitors in the treatment of elderly women with metastatic breast cancer

Stefan Glück [a,*], Gunter von Minckwitz [b], Michael Untch [c]

[a] Department of Medicine, Division of Hematology/Oncology, Sylvester Comprehensive Cancer Center, University of Miami, Leonard M. Miller School of Medicine, 1475 NW 12th Ave, Miami, FL 33136, USA
[b] German Breast Group, c/o GBG Forschungs GmbH, Neu-Isenburg and University Women's Hospital, Frankfurt, Germany
[c] Clinic for Gynecology, Gynecologic Oncology and Obstetrics, HELIOS Klinikum Berlin-Buch, Berlin, Germany

ARTICLE INFO

Article history:
Received 3 May 2012
Received in revised form
26 October 2012
Accepted 17 December 2012

Keywords:
Aromatase inhibitors
Breast cancer
Elderly
Exemestane
Metastatic
Tamoxifen
Antineoplastic agents
Hormonal

ABSTRACT

The proportion of elderly women in the population is rising, and in tandem, the incidence of breast cancer rises with age. Because of health and tolerability concerns, as well as life expectancy, physicians may be reluctant to advise a standard treatment regimen for elderly patients with metastatic breast cancer. To elucidate this issue, we performed a literature review of clinical studies that included women with metastatic breast cancer who were over the age of 65. Our results show that although little clinical evidence exists, what is available suggests that standard treatment is tolerated and beneficial for patients meeting certain criteria. A geriatric assessment may identify specific patient groups (independent, dependent, or frail) and thereby guide treatment. Treatment recommendations for elderly patients with metastatic breast cancer are sparse, although first-line endocrine treatment, usually aromatase inhibitors or tamoxifen, is recommended for hormone-sensitive disease. In general, the evidence from clinical studies suggests that aromatase inhibitors are more effective than either tamoxifen or megestrol acetate as first- or second-line treatment in postmenopausal women with metastatic breast cancer. Ultimately, quality of life, treatment effects, and comorbidities are important aspects in this population and may guide treatment choice. To provide evidence-based treatment guidance, future clinical trials should include more patients over the age of 65 years.

Introduction

The incidence of breast cancer (BC) increases with age until menopause; thereafter, incidence remains stable. In the United States and Europe, overall incidence of BC has declined since 2002, and BC-specific deaths have been declining for the past decade; however, the proportion of elderly women with BC is rising.[1–6] Median age at diagnosis is 61 years in the United States and 63 years in Europe.[7,8] Moreover, diagnosis of metastatic BC (mBC) is more frequent among women >75 years than among women 65–75 years.[9]

For cancer patients, "elderly" is generally considered ≥65 or ≥70 years of age, but definitions used in clinical trials vary from ≥60 to ≥70 years.[4,10] However, regardless of definition, approximately half of BC patients are considered elderly based on median age at diagnosis and are underrepresented in clinical trials. For example, in Southwest Oncology Group (SWOG) BC trials, it was estimated that <10% of patients were ≥65 years.[10] Patients ≥65 years are often excluded from BC clinical trials either because of eligibility criteria or physician perceptions that older patients are less able to tolerate standard therapies.[11] However, a case-comparison study of chemotherapy for mBC showed that patients ≥70 years had similar outcomes and side effects as younger patients.[12] Few trials have specifically enrolled elderly patients. Therefore, data to support evidence-based guidelines for management of mBC in elderly women are limited, resulting in different patterns of care and/or suboptimal treatment.[6,10]

This review of published clinical studies including women aged ≥65 with mBC focuses on factors influencing treatment decisions in elderly patients and available evidence supporting use of aromatase inhibitors (AIs) in this setting.

Factors affecting treatment of metastatic breast cancer in elderly women

Although age is not an independent prognostic factor, BC in elderly women is frequently less aggressive than in younger

* Corresponding author. Tel.: +1 305 243 6264; fax: +1 305 243 4047.
E-mail address: sgluck@med.miami.edu (S. Glück).

0960-9776/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.breast.2012.12.015

women, and the tumors often display more favorable biologic characteristics. Elderly patients more often have estrogen and progesterone receptor-positive tumors (~80%) versus younger women (range, 42%–77%).[13] Although bone metastasis is more common in elderly patients, incidence of visceral metastasis is similar to that of younger patients.[9] Various factors should be considered during treatment decisions for elderly BC patients (Table 1). Improved tumor evaluation and risk assessment are also needed to determine appropriate therapy for elderly patients. Indeed, receptor status of a recurrent metastatic tumor may be different from the primary tumor and require separate biopsy for treatment guidance.[14–19]

Age-related physiologic factors

Older patients may have cognitive impairment, compromised gastrointestinal function, first-pass metabolism, or renal function affecting pharmacokinetics/pharmacodynamics (PK/PD) of drugs. Decreased bone marrow reserve increases hematologic toxicity risk.[4] Although there are small or no chemotherapy PK differences between patients aged ≥65 years and younger patients,[20] differences in PD are common, with increased risk for toxicities in elderly patients. However, older patients can benefit from standard, dose-intense chemotherapy,[21,22] and chemotherapy doses can be modified without compromising efficacy.[23,24] Dehydration related to decreased thirst reflex may become life-threatening in the presence of diarrhea or prolonged vomiting,[10] and the resulting electrolyte imbalance may have more serious consequences in elderly patients with cardiovascular conditions. Therefore, antiemetics may be even more important in elderly patients, although current antiemetic guidelines do not offer specific recommendations for this population.[25–27]

Comorbid conditions

Compared with younger patients, elderly (≥65 years) BC patients have more comorbid conditions and a wider range of comorbidities that can affect life expectancy, physiologic reserves, and ability to tolerate treatment.[4,10] Among women >67 years diagnosed with BC (any stage), the most common comorbidities are diabetes, chronic obstructive pulmonary disease, cardiovascular diseases, and cerebrovascular disease.[28] Cardiovascular disease, in particular, is an important competing cause of death in elderly patients with mBC.[29] Therefore, drugs with significant cardiovascular toxicity, such as anthracyclines, are of concern in elderly patients.[4] Combining anthracyclines with trastuzumab or paclitaxel may also increase risk of cardiotoxicity in patients with mBC, although a liposomal anthracycline might provide lower cardiotoxicity risk.[30,31] Obesity is another factor associated with all-cause and BC-specific mortality among postmenopausal women.[32]

Table 1
Factors to consider in disease management of metastatic breast cancer in elderly patients.

Physiologic age
Physiologic reserves
Renal and hepatic function
Thirst reflex
Cognitive decline
Comorbid conditions
Cardiovascular diseases
Diabetes/insulin resistance
Pulmonary diseases
Dementia
Bone health
Life expectancy
Number and extent of comorbid conditions

Breast cancer may increase risk of osteoporosis and fractures in elderly women,[33,34] and many BC treatments, except tamoxifen, reduce bone mineral density.[35] In general, therapy with bone-modifying agents is recommended.[35–40] Hypertension and thromboembolism are other concerns, especially with tamoxifen or bevacizumab treatment. However, none of the studies that include tamoxifen in advanced BC have subanalyses by age; therefore, risk of thromboembolism from tamoxifen treatment cannot be determined.[41] A recently validated algorithm that includes specific factors for women, such as tamoxifen and hormone replacement therapy, can estimate risk of venous thromboembolism at 1 and 5 years.[42]

Life expectancy

Generally, in BC patients with distant metastases, the 5-year survival rate is <25% (for patients ≥50 years).[3,43] However, comorbid conditions in women aged 65–70 years have a very pronounced effect on survival (Fig. 1).[4] Therefore, elderly patients should have a geriatric assessment for likelihood of death from BC. Although overall likelihood of death from BC decreases with advancing age, this is not the case with distant disease.[44] Among patients aged ≥70 years with distant mBC, BC-specific death accounted for 75% of the 5-year death rate following diagnosis. Even among patients ≥70 years with regional disease (estrogen receptor-positive), BC-specific death accounted for 39% of the 5-year death rate following diagnosis (63% among patients with estrogen-negative tumors). Furthermore, metastasis site is an independent prognostic factor for survival in elderly patients, similar to younger patients.

Assessments for elderly patients with metastatic breast cancer to guide disease management

Advanced age and declining physical performance in elderly patients may lead physicians to decrease their use of diagnostic tests, which may result in suboptimal treatment for mBC.[45–47] A comprehensive geriatric assessment provides the best estimate of functional age; this should include a number of evaluations before deciding on a treatment course[4,19,43,45,48–50] (Table 2).[50]

The assessment of functional independence provides information on survival and tolerance of adverse effects from cancer treatment.[50] The need for assistance in certain activities of daily living (ADL) is associated with decreased tolerance for chemotherapy. Determining socioeconomic conditions and cognition evaluates the patient's ability to comprehend and adhere to treatment.[50] This assessment can also reveal frailty (dependence in ≥1 ADL) and exhaustion of functional reserves.

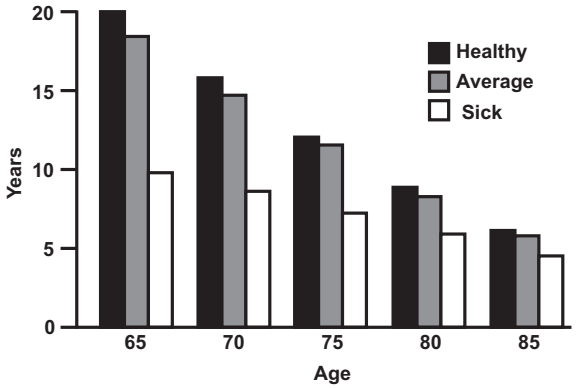

Fig. 1. Life expectancy by general health status in older patients with breast cancer. Reprinted with permission from *JNCCN–Journal of the National Comprehensive Cancer Network*.