Current Targeted Therapies in Breast Cancer: Clinical Applications in the Elderly Woman

JEAN-PHILIPPE SPANO,^a CLAIRE FALANDRY,^b PASCAL CHAIBI,^c GILLES FREYER^d

^aGroupe Hospitalier de la Pitié-Salpêtrière, Département d'Oncologie Médicale du Prof. David Khayat, Paris, France; ^bUniversité de Lyon, Hospices Civils de Lyon, Service de Gériatrie, Centre Hospitalier de Lyon Sud, Pierre Bénite, France; ^cGroupe Hospitalier de la Pitié-Salpêtrière Charles Foix, Pôle Hospitalier de Gériatrie, Ivry, France; ^dService d'Oncologie Médicale, Centre Hospitalier de Lyon Sud, Hospices Civils de Lyon, Pierre-Bénite, France

Key Words. Targeted therapy • Breast cancer • Elderly woman • Recommendations

Disclosures

Jean-Philippe Spano: None; **Claire Falandry:** None; **Pascal Chaibi:** None; **Gilles Freyer:** None.

Section Editor **Matti Aapro** discloses no financial relationships relevant to the content of this article.

Section Editor **Arti Hurria** discloses a consulting/advisory role with Amgen, Genentech, and GTX; and research funding received from Celgene and GlaxoSmithKline.

Section Editor **Hyman B. Muss** discloses a consulting relationship with Pfizer, Amgen, Roche, Bristol-Myers Squibb, Boehringer-Ingelheim, Sandoz, Abraxis, and Eisai.

Reviewer "A" discloses no financial relationships.

The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. On the basis of disclosed information, all conflicts of interest have been resolved.

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Include geriatric assessment into oncologic practice to describe patients and to evaluate the real benefit/risk ratio of any adjuvant treatment.
2. Describe the actual risk of association of erythropoiesis-stimulating agents with bevacizumab.

ABSTRACT

The incidence of breast cancer is two to three times higher in women aged ≥ 65 years than in the whole population, whereas their mortality rate is threefold to fourfold higher. Targeted therapies allow significantly longer disease-free survival times. Nevertheless, in an elderly population, these treatments need to be pre-

scribed with caution. This paper reviews the treatments of breast cancer in the elderly, and the issues of targeted therapies and their toxicities.

Patients with human epidermal growth factor receptor (HER)-2⁺ breast cancer benefit from trastuzumab; although cardiotoxic effects are observed in <5% of pa-

Correspondence: Jean-Philippe Spano, M.D., Ph.D., Service d'Oncologie Médicale, Hôpital de la Pitié Salpêtrière, F-75013 Paris, France. Telephone: 33-0-1-42-16-04-72; Fax: 33-0-1-42-16-04-69; e-mail: jean-philippe.spano@psl.aphp.fr Received October 20, 2010; accepted for publication May 13, 2011; first published online in *The Oncologist Express* on June 24, 2011. ©AlphaMed Press 1083-7159/2011/\$30.00/0 doi: 10.1634/theoncologist.2011-0028

tients when given alone, they affect ~25% of patients when combined with anthracyclines. Bevacizumab leads to a longer progression-free survival time and lower risk for progression in patients with metastatic breast cancer when added to paclitaxel or docetaxel. Although generally well tolerated, it is associated with a higher risk for arterial thromboembolism and hypertension. Lapatinib is approved for the treatment of advanced or metastatic breast cancer in patients not responding to trastuzumab, combined with capecitabine chemotherapy. The most frequent side effects concern the gastrointestinal system and dermatologic symptoms.

The life expectancy of breast cancer patients should be taken into account to determine the appropriateness of treatments. The quality of life of elderly cancer patients must be assessed with an appropriate tool. Older patients exhibit greater vulnerability, suggesting identification and exclusion of patients at high cardiac risk.

Future recommendations for the treatment of elderly women with breast cancer should include a multidisciplinary approach and a global geriatric assessment before treatment with anti-HER-2 therapy or bevacizumab. *The Oncologist* 2011;16:1144–1153

INTRODUCTION

The breast is the most common localization of tumors in women, and breast cancer is the leading cause of cancer mortality in women worldwide. The crude incidence of breast cancer is two to three times higher in women aged ≥ 65 years than in the whole population, whereas their breast cancer mortality rate is threefold to fourfold higher [1]. Because demographic projections predict a great increase in people aged >65 years in the next decades, and consequently a rise in cancer incidence and mortality [2], it seems important to evaluate the benefit–risk ratio of each therapeutic alternative for the elderly woman with breast cancer. Elderly-specific trials are needed for the adaptation of treatment guidelines because of age-related specificities in tumor biology and treatment tolerance and efficacy. As novel products continuously emerge from drug research, their assets and drawbacks have to be considered in the context of elderly patients.

This review aims to actualize the knowledge about breast cancer in the elderly woman, and to address the issues of novel targeted therapies and their specific toxicities.

WHICH DEFINITION FOR AN ELDERLY WOMAN?

The age of 70 is commonly adopted as the threshold value for elderly patients. Screening for breast cancer through systematic mammography campaigns, as practiced in Europe, often targets 50- to 70-year-old women. Above 70, individual breast examination depends on medical indication, patient will, and presumed life expectancy, both in Europe and in North America [1].

Age is related to declining function in organ systems, impairing life expectancy as well as cancer treatment tolerance. However, interindividual variability is important, and age should not be considered as a unique criterion for decision making [3]. In the interest of patients, it appears crucial to reconcile oncologists, focused on curing cancer, and geriatricians, seeking to prevent functional decline. Rather

than age, a comprehensive geriatric assessment (CGA) should be favored to gather information about one's capacity to endure cancer treatment. Balducci and Extermann recommended that a CGA should be used for people aged ≥ 70 [3]. The CGA includes assessment of comorbidities, socioeconomic conditions, functional dependence, emotional and cognitive background, overall frailty, and life expectancy. All those elements help the medical team to estimate the risk–benefit ratio of the treatment and the patient's capacity to adhere to the treatment. A four-stage classification derived from the CGA has been proposed—primary, intermediate, secondary or frailty, and tertiary or near to death—together with clinical descriptions and therapeutic implications [4]. Rather than chronological age, oncologists may take into account the functional age of their patients, but they regrettably underuse CGA or comorbidity scoring [5]. The ability to complete activities of daily living (ADL) and instrumental ADL (IADL) reflects one's skill at maintaining independence at home and among the community. As part of the functional status assessment, ADL and IADL are displayed as relevant criteria for older adults with cancer, because they are predictive of surgery complications, treatment-related toxicity, pain severity, and psychological distress [2].

Comorbidities and functional status interfere with cancer prognosis and treatment choices, particularly for elderly patients. Because they are more often affected by interfering health issues, half of them die from noncancer-related causes [6]. The mortality rate from causes other than breast cancer is 20-fold higher in women with three or more comorbidities than in women without associated comorbid conditions. Furthermore, the mortality rate was found to be independent of age, disease stage, tumor characteristics, and social factors [7]. A prospective study followed women aged ≥ 70 for 7 years after they were diagnosed and treated for a stage I or stage II breast cancer. That study showed that, among those who died, the overall breast cancer death

rate was 32.5%. This rate fell to 23.5% for women aged >80 years at the time of diagnosis [8]. Comorbidities, particularly, previous cancer and diabetes, impair the 5-year survival rate [9]. Furthermore, treatments prescribed to control concomitant diseases can also enhance the risk for treatment-related complications, with a potential adverse influence on survival [5].

In addition, frailty has been shown to be associated with biological markers, such as the proinflammatory cytokine interleukin-6 or C reactive protein, which are also prognostic markers for cancer [2]. Biological markers could therefore be potentially useful to complete the geriatric assessment, although their impact on treatment efficacy and tolerance has not been documented yet.

WHICH TUMOR CHARACTERISTICS IN THE ELDERLY?

On average, elderly patients present more favorable biologic tumor parameters, but are diagnosed with larger and more advanced tumors and with more involved lymph nodes [10]. Around 80% of breast cancer occurring in women aged >70 years is hormone dependent and weakly aggressive. But nearly one in five cases is classified as a grade 3 tumor, characterized by a high proliferation rate, large size, and nodal invasion potential [11]. However, the survey cohort from the American Surveillance, Epidemiology, and End Results (SEER)–Medicare database of nearly 50,000 women aged >67 years did not show any difference in tumor hormone receptor expression between women aged >80 and younger women [12].

Histological studies found that 7%–28% of elderly patients with breast cancer were human epidermal growth factor receptor (HER)2⁺ [11, 13, 14], and that expression of HER-2 correlated with high nuclear grade tumors [14]. Although most patients were positive for estrogen receptor α and benefit from primary endocrine therapy, 8% of them were found to be HER-2⁺ and had a shorter progression-free survival (PFS) interval [15].

Whether or not tumors of the elderly are less aggressive than those of young women remains uncertain. This appears to be true for women aged ≥ 70 years compared with those aged <40, but not compared with those in the 40- to 69-year-old age range [8]. A retrospective study examining adherence to breast cancer guidelines in a population of women aged ≥ 70 years underlined that the decision to use adjuvant chemotherapy was not related to CGA results, whereas age >75 years was an independent variable inversely associated with receiving chemotherapy. Therefore, appropriate treatment was given to 63% of Balducci's class I patients, and to only 36% of class II patients [16]. The American SEER–Medicare survey cohort also showed

that age was the main variable associated with the choice of treatment. The oldest of the old (>80 years) were more likely to have only breast-conservative surgery although their tumor characteristics were not different from those of others [12]. Elderly patients deserve adequate treatment based on tumor biology, and should not receive less effective treatment just because of age alone.

POOR CLINICAL DATA FOR THE ELDERLY

One breast cancer in three in Northern America, and one in 2.3 in Europe, affects a woman aged >65 years [1], but clinical trials scarcely include this population, although age is not an exclusion criterion (Table 1). A meta-analysis focusing on the rate of enrollment in oncology clinical trials of patients aged >65 years in 1993–1996 in the U.S. highlighted their huge underrepresentation. This was dramatically true in the field of breast cancer: 9% of patients included in trials belonged to the elderly class, whereas they represented 49% of the breast cancer population [17]. More recently, only 16% and 15% of women included in the Herceptin® Adjuvant (HERA) and National Surgical Adjuvant Breast and Bowel Project (NSABP)-B31 phase III studies, respectively, were aged >60 years [18, 19]. Pivot et al. [20] reviewed the tolerance of bevacizumab in the first-line treatment of elderly patients with metastatic breast cancer in combination with taxanes, either docetaxel or paclitaxel, in the Avastin® and Docetaxel (AVADO) and MO19391 trials. Similarly low proportions of elderly patients were reported for both the AVADO and MO19391 trials, with 17.3% of women aged ≥ 65 years and 8% of women aged >75 years. In the 65- to 85-year-old subgroup, no significant difference in favor of any treatment regimen was identified, probably because of the small sample size. However, according to these studies, comorbidities and associated risks are crucial factors to take into account for the choice of treatment.

There is a lack of data from studies specifically designed for elderly populations, which would be able to address the question of efficacy and tolerability of therapeutic choices. Clinical data are commonly derived from subgroup analysis of phase III studies. Therefore, recommendations are not based on level I evidence. Patients and their families are often reluctant to enroll in clinical trials because of misconceptions, and efforts in explaining by geriatricians, in tight collaboration with oncologists, should enhance the opportunity to include elderly patients in clinical trials [1, 17]. The most important overall limits to inclusion of elderly patients in clinical trials are the reluctance of investigators and the inclusion and exclusion criteria usually defined by the investigative team of the trial.

Table 1. Sample size attributed to elderly women in various clinical trials

Trial	Patient age (yrs)	Sample size of elderly (% of total population)	Study
AVADO	≥65	17%	Pivot et al. (2009) [20]
MO19391	≥70	8%	Pivot et al. (2009) [20]
HERA	≥60	16%	Piccart-Gebhart et al. (2005) [18]
NSABP-B31	≥60	15%	Romond et al. (2005) [19]
ECOG 2100	65–85	22%	Miller et al. (2007) [24]

Abbreviations: AVADO, Avastin® and Docetaxel; ECOG, Eastern Cooperative Oncology Group; HERA, Herceptin® Adjuvant; NSABP, National Surgical Adjuvant Breast and Bowel Project.

WHICH TARGETED THERAPIES FOR BREAST CANCER?

Several new targeted molecules have enriched the therapeutic armamentarium against breast cancer in the past decade. Even though their action focuses on malignant cells, greatly restricting their toxicity profile compared with classic cytotoxic drugs, some side effects still have, however, been mentioned.

Trastuzumab is a monoclonal antibody aimed against HER-2, used in cases of overexpression of the *HER-2* gene. The efficacy of trastuzumab in breast cancer patients has been ascertained in both the metastatic [21] and adjuvant [18, 19] settings. All patients with HER-2⁺ tumors potentially benefit from trastuzumab, but cardiotoxicity has been reported to be the major side effect of this treatment. Limited to <5% of patients when given alone, cardiotoxicity affects ~25% of patients when combined with anthracyclines for metastatic disease [22]. Gastrointestinal side effects have also been mentioned [23].

Bevacizumab is a monoclonal antibody that binds to vascular endothelial growth factor (VEGF), blocking VEGF binding to high-affinity receptors and preventing its proangiogenic effect. It has been shown to lead to higher PFS and objective response rates [24, 25] and a lower risk for progression [24, 26] in metastatic breast cancer patients when added to paclitaxel or docetaxel; such combinations produce longer disease-free survival times [26]. Bevacizumab is generally well tolerated. However, a meta-analysis of the use of bevacizumab in patients with various metastatic tumors revealed that it was associated with a higher risk for arterial thromboembolism [27]. A review of

bevacizumab side effects in patients with metastatic solid tumors showed that hypertension was the most frequently encountered adverse event [28].

Lapatinib inhibits the tyrosine kinase activity of HER-2 and has received approval for use in advanced or metastatic breast cancer patients not responding to trastuzumab, combined with capecitabine chemotherapy [29]. Its tolerance profile is good; the main side effects concern the gastrointestinal system (diarrhea) and dermatologic symptoms. Some patients develop impairment of the left ventricle ejection fraction, but the prevalence of this adverse event remains limited (~0.5%) [30].

The mechanism of action of pertuzumab, erlotinib, and neratinib (molecules interfering with growth signaling pathways) suggests that they should be noteworthy in the treatment of breast cancer [31, 32]. The product coded TDM1 combines trastuzumab with maytansine. A phase II study investigated the safety and efficacy of TDM1 in patients with HER-2⁺ metastatic breast cancer who were previously treated with trastuzumab alone. With a follow-up ≥12 months among 112 treated patients, the objective response rate by independent assessment was 25.9% (95% confidence interval [CI], 18.4%–34.4%) [33, 34].

ADJUVANT THERAPY

A presentation during the joint congress of the European Society for Medical Oncology and European Multidisciplinary Cancer Congress in September 2009 showed retrospective results from a 49-patient cohort aged ≥70 years being treated with trastuzumab, in the adjuvant or metastatic setting, with various chemotherapy agents used in combination. A multivariate logistic regression analysis associated cardiotoxicity with two significant risk factors: history of cardiac disease and diabetes [35].

Combined results of the NSABP-B31 and North Central Cancer Treatment Group (NCCTG) N9831 clinical trials showed evidence of a great benefit with 1-year adjuvant treatment with trastuzumab after chemotherapy in women with HER-2⁺ breast tumors. However, patients with impaired cardiac function were excluded from trastuzumab treatment, which led to a lower incidence of cardiac complications [19]. Gathering data from four major trials including >13,000 women, Baselga et al. [36] showed a slightly higher incidence of cardiac events among patients receiving trastuzumab. However, the incidence of heart failure remained low (≤3.3%) and it was reversible in most cases. In the same way, significantly more patients receiving 1 year of trastuzumab in the HERA trial experienced congestive heart failure (2.2%) and a decrease in left ventricular ejection fraction (7.1%), but these events were not life threatening [18]. Recently published intermediary re-

sults confirmed that long-term toxicity remains low and is mostly easy to manage after 3.6 years of mean follow-up, although almost all patients received anthracyclines [37]. Therefore, this cardiac effect of trastuzumab should not weigh much on the balance risk pan, in light of the great benefits of the treatment.

The International Society of Geriatric Oncology (SIOG) calls for more caution. Collecting information from elderly-specific clinical studies and elderly subgroup analyses of larger trials, a review of clinical data recently showed that anthracyclines are the most effective drugs to avoid breast tumor recurrence (Fig. 1). Nevertheless, they are also associated with a higher incidence of cardiotoxicity in older patients. The SIOG expert position suggests taking cardiac risk factors into account, to prematurely manage cardiac side effects, and to avoid anthracyclines and trastuzumab combinations. It also advises experimenting with less cardiotoxic formulations, such as liposomal anthracyclines, and other anti-HER-2 agents such as lapatinib. Finally, it warns against the risk for overtreatment in the elderly [38].

Combination of anthracyclines and trastuzumab in the treatment of women with HER-2⁺ primary breast cancer is currently being investigated in the Breast International Group 01-06/Epidermal Growth Factor 106903 study [39]. Nevertheless, this combination remains currently prohibited, and the above trials have not yet shown final efficacy and safety data.

Avoiding anthracyclines, the combination of trastuzumab with taxanes produced a 4.2% cardiac event rate in a phase II study including 260 patients. After a 7-year follow-up, this combined treatment displayed good efficacy and tolerance patterns, even when considering the ≥ 65 -year-old subgroup [40]. No specific data exist for the elderly women because of the minor representation of this age category in the clinical trials previously mentioned. Therefore, breast cancer treatment in women aged >65 years is mainly based on data collected from trials in younger women [41]. Experts agree on recommending trastuzumab with adjuvant chemotherapy in cases of hormone receptor-negative and HER-2⁺ tumors, although evidence for a specific benefit is lacking.

Slamon et al. [42] conducted a phase III randomized trial comparing docetaxel-carboplatin-trastuzumab with docetaxel-trastuzumab in 263 patients with HER-2-amplified metastatic breast cancer. Patients were randomly assigned to receive trastuzumab plus docetaxel or trastuzumab plus carboplatin and docetaxel. There was no significant difference between treatments in terms of the primary endpoints time to progression (median, 11.1 months and 10.4 months, respectively; hazard ratio, 0.914; 95% CI, 0.694–1.203; $p = .57$), response rate (72% for

both groups), and overall survival (median, 37.1 months and 37.4 months, respectively; $p = .99$). Grade 3 or 4 adverse effects for docetaxel-trastuzumab and docetaxel-carboplatin-trastuzumab were neutropenic-related complications, thrombocytopenia, anemia, sensory neuropathy, fatigue, peripheral edema, and diarrhea. Absolute left ventricular ejection fraction decline $>15\%$ was seen in 5.5% of patients in the docetaxel-trastuzumab arm and 6.7% of patients in the docetaxel-carboplatin-trastuzumab arm [42].

Pierga et al. [43] assessed the antitumor activity of sequential epirubicin-cyclophosphamide followed by docetaxel with the randomized addition of celecoxib in HER-2⁻ patients ($n = 220$) or trastuzumab in HER-2⁺ patients ($n = 120$) with stage II and stage III breast adenocarcinoma. In the HER-2⁻ group, the pathologic complete response (pCR) rates (grade 1 and 2 of Chevallier's classification) were 11.5% and 13% in patients treated without and with neoadjuvant celecoxib, respectively. In the HER-2⁺ group, the pCR rate reached 26% in those who received neoadjuvant trastuzumab, versus 19% in the others. There was no unexpected toxicity, no cardiac toxicity, and no toxic death. Patients with triple-negative breast cancers experienced the highest pCR rate of 30% [43].

The cardiovascular health of patients should be carefully assessed. Trastuzumab alone is not recommended [44].

METASTATIC SITUATION

Trastuzumab has also been effectively used in patients with metastatic breast cancer overexpressing HER-2, used alone or in combination with chemotherapy agents [21]. As in adjuvant therapy, the main side effect is cardiotoxicity, particularly when combined with or following anthracyclines, for patients with pre-existing cardiac dysfunction and in the elderly subgroup [45, 46]. In the phase III Trastuzumab in Dual HER2 ER-Positive Metastatic Breast Cancer study, the combination of trastuzumab with anastrozole for HER-2⁺ hormone receptor-positive metastatic breast cancer patients was more effective than anastrozole alone, but more adverse and serious adverse events occurred in the combined treatment group (28% versus 16%). Patients in the trastuzumab plus anastrozole arm experienced a significantly longer PFS interval than patients receiving anastrozole alone (hazard ratio, 0.63; 95% CI, 0.47–0.84; median PFS, 4.8 months versus 2.4 months; log-rank $p = .0016$). In patients with centrally confirmed hormone receptor positivity ($n = 150$), the median PFS times were 5.6 months and 3.8 months in the trastuzumab plus anastrozole and anastrozole alone arms, respectively (log-rank $p = .006$). Overall survival in the hormone receptor-positive populations showed no statistically significant difference by treatment;

Figure 1. Analyses of disease-free survival according to subgroup.

Abbreviations: BCIRG, Breast Cancer International Research Group; FinHER, Finnish Herceptin®; HERA, Herceptin® Adjuvant.

Based on information from Piccart-Gebhart MJ, Procter M, Leyland-Jones B et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005;353:1659–1672.

however, 70% of the patients in the anastrozole alone arm crossed over to receive trastuzumab after progression on anastrozole alone [47]. At the moment, data concerning elderly patients are missing to assess the tolerance of trastuzumab combined with hormone therapy.

Lapatinib exhibits a good overall tolerance, but no study has yet been dedicated to elderly women. In the Lapatinib Expanded Access Program, designed to enroll patients in countries where lapatinib had not yet receive regulatory approval, women received capecitabine plus lapatinib for advanced or metastatic breast cancer, as second- or third-line treatment, after trastuzumab failure. This open-labeled cohort of 4,285 patients showed that the most common side effects were diarrhea (9.7%), vomiting (4.3%), and nausea (2.4%). Cardiotoxicity was scarcely encountered (0.5% of patients with left ventricle ejection fraction reduction), although these women could have been previously treated with anthracyclines [30]. Accordingly, a pooled analysis of 44 clinical studies collecting data from 3,689 patients revealed a 1.6% rate of cardiac events after lapatinib administration (2.2% with previous anthracyclines); these were mostly asymptomatic and reversible [48]. When women coexpressing HER-2 and hormone receptors were treated with letrozole as first-line therapy for metastatic breast cancer, the addition of lapatinib led to a longer PFS interval (8.2 months, compared with 3.0 months for letrozole alone), a higher objective response rate, and a higher clinical benefit rate. Moreover, lapatinib was rather well tolerated because it just induced additional adverse events of grade 1 or grade 2 (mainly diarrhea or rash) [49]. Some recent data suggested that the combination of lapatinib with

trastuzumab leads to a significantly longer overall survival time than with single-agent lapatinib in women with metastatic breast cancer [50].

Other molecules are currently under development in order to treat patients not responding to trastuzumab, or to avoid trastuzumab-induced cardiotoxicity. The combination of trastuzumab with the tyrosine kinase inhibitor erlotinib displayed favorable preliminary results [31]. Studies examining the efficacy and tolerance of trastuzumab plus pertuzumab, a monoclonal antibody that inhibits HER-2 dimerization, were designed with similar concerns [32]. Neratinib, an oral irreversible tyrosine kinase inhibitor, gave promising results and no cardiologic side effects in a phase II study [32]. All these well-tolerated new targeted molecules will probably complete the fan of therapeutic choices for elderly patients.

The use of bevacizumab in metastatic breast cancer patients remains controversial. Following the pivotal Eastern Cooperative Oncology Group (ECOG) 2100 trial, bevacizumab was approved for use as first-line therapy in patients with advanced breast cancer. Recently, the U.S. Food and Drug Administration voted unanimously against this licensed indication from the product's labeling. This is because two other trials were conducted (AVADO and RIBBON-1) and both showed a statistically significant longer PFS duration, although of a much smaller magnitude than was seen in the ECOG 2100 study. After meta-analyzing two randomized bevacizumab trials that addressed somewhat different populations (a pure second-line population in RIBBON-2 [50] and a heavily pretreated population in the Miller et al. [24] trial), the overall response rate

(relative risk, 1.63; 95% CI, 1.02–2.62; $p = .04$) and PFS duration (hazard ratio, 0.85; 95% CI, 0.73–0.98; $p = .03$) were significantly greater with the addition of bevacizumab to chemotherapy [51].

A retrospective study on 1,745 patients showed a risk for an arterial event (angina, cerebrovascular accident, cardiac stroke) three times higher in patients aged ≥ 65 years than in younger patients (3% versus 1%) [31]. The age subgroup analysis of the ECOG E2100 trial demonstrated superior efficacy for bevacizumab plus paclitaxel than for paclitaxel alone, although this was not significant in the 65- to 85-year-old subgroup [24]. Indications should take into account comorbidities and associated risk factors (hypertension, hypercholesterolemia, history of arterial event) [52]. In a retrospective analysis of the AVADO study focusing on elderly patients (aged ≥ 65 years), the addition of bevacizumab was generally well tolerated by patients with metastatic breast cancer. No substantial additional side effects of taxane treatment were observed [20]. In a meta-analysis, Bennett et al. [53] found a 57% higher risk for thromboembolism (risk ratio, 1.57) resulting from treatment with erythropoiesis-stimulating agents (ESAs). In elderly women with breast cancer treated using bevacizumab and in spite of the few data available, the risk for thromboembolism is approximately twofold greater. It seems, therefore, that the combination of an ESA with bevacizumab in elderly patients must be considered with a lot of caution to avoid major side effects.

SIDE EFFECTS OF TREATMENTS

Breast cancer clinical trials aim at assessing the potential of new therapies to offer a better life expectancy to patients, but also aim to improve patient quality of life during breast cancer treatment. Side effects are one of the major concerns when developing new therapies because they are directly linked to patient quality of life (Table 2).

Cardiotoxicity is one of the most common side effects of current therapies. A 5% incidence of cardiotoxicity was reported in the HERA trial, whereas a 4.1% incidence was reported in the NSABP B-31 trial and a 2.9% incidence was reported in the NCCTG N9831 trial. In addition, cardiovascular-related adverse events (hypertension, left ventricle ejection weakening, congestive heart failure, etc.) are frequently experienced by patients. Therefore, assessment of the cardiovascular status of the patient is recommended to be taken into account in the choice of therapy. Prospective treatments (neratinib, lapatinib, pertuzumab) are currently being studied in order to limit these life-threatening side effects.

In a recent paper, Costa et al. [54] reviewed cardiac safety data from adjuvant trastuzumab trials (NSABP B-31, NCCTG N9831, Breast Cancer International Research Group 006, and

PACS [Programme d'Actions Concertées Sein] 04). The addition of trastuzumab to adjuvant chemotherapy led to a significantly lower relapse risk (24% versus 58%) in five of the six trials. In NSABP B-31/NCCTG N9831, 5.0%–6.6% of patients who received doxorubicin and cyclophosphamide were not eligible to receive trastuzumab. The rate of cardiac adverse events was highest in the anthracycline-containing trastuzumab arms (1.9%–3.8%) and lowest with the regimen with docetaxel, carboplatin, and trastuzumab (0.4%). Incorporation of trastuzumab into anthracycline and nonanthracycline adjuvant chemotherapy regimens has substantially improved outcomes in patients with HER-2⁺ early breast cancer. Patients treated with the docetaxel, carboplatin, and trastuzumab regimen had the lowest rates of cardiac dysfunction, but uncertainty exists regarding its relative efficacy compared with anthracycline-containing trastuzumab regimens [54].

CONCLUSION

The main side effects of breast cancer–targeted therapies affect the heart and the vascular system, with the known cardiotoxicity of trastuzumab and the hypertensive action of bevacizumab. They are cumulative with the cardiotoxic effects of anthracyclines when used before or with these monoclonal antibodies. In the interest of elderly patients, oncologists and geriatricians should tailor their therapeutic approaches to optimize the benefit–risk ratio. The assessment of individual health issues, particularly related to the cardiovascular system, is crucial to measure the constraints of this heterogeneous class of patients and to adequately orient treatment choices. Further trials dedicated to the elderly population may help to elucidate the efficacy and toxicity of these novel targeted therapies and avoid both underuse and overtreatment.

The life expectancy and overall survival probability of breast cancer patients treated using adjuvant therapy should be taken into account to determine the appropriateness of treatments. The quality of life of elderly cancer patients must be assessed with an appropriate tool, such as that described by Lee et al. [55], on the basis of functional status. According to Brain [38], comorbidities such as hypertension, diabetes, coronary disease, and many others are frequent in elderly populations. Because several adjuvant cancer drugs like anthracyclines exhibit short- and long-term cardiotoxic effects, their use in the elderly, who already have an elevated risk for side effects and comorbidities, must be considered cautiously. Regarding the analysis reported by Brain [38], anthracycline-based adjuvant therapy reduces disease recurrence in elderly breast cancer patients. Nevertheless, older women have a higher incidence of cardiotoxic side effects together with a lower relative survival rate. This confirms the vulnerability of

Table 2. Side effects of various therapies and appropriate recommendations for a better breast cancer treatment

Trial	Therapy	Side effects	Recommendation	Study
HERA	Trastuzumab	<ul style="list-style-type: none"> ● Congestive heart failure (2.2%) ● Impairment of left ventricle ejection function (7.1%) ● Cardiotoxicity (5%) 	<ul style="list-style-type: none"> ● Not recommended with anthracyclines (side effects greater, at 25%) ● Used when anthracyclines are unsuitable ● Not recommended alone 	Piccart-Gebhart et al. (2005) [18] Slamon et al. (2001) [21] Tu et al. (2009) [22]
	Trastuzumab + chemotherapy	Severe cardiotoxicity (0.5%)	Life expectancy one third longer than with chemotherapy alone	Piccart-Gebhart et al. (2005) [18] Romond et al. (2005) [19]
TanDEM	Trastuzumab + anastrozole	28% more side effects than with anastrozole alone	Take into account cardiovascular and overtreatment risks	Kaufman et al. (2009) [47]
	Trastuzumab + pertuzumab	Minimal cardiotoxicity	Pertuzumab is recommended in patients in whom trastuzumab failed	Baselga et al. (2010) [32]
NSABP-B31 N9831	Trastuzumab + paclitaxel	Cardiotoxicity in 4.1% (NSABP-B31) versus 2.9% (N9831) of patients	50% lower risk for death	Romond et al. (2005) [19]
AVADO	Bevacizumab	Higher risk for an arterial event (3%) than in younger patients (1%)		Pivot et al. (2009) [20] Miller et al. (2007) [24] Valachis et al. (2010) [25] Scappaticci et al. (2007) [27]
MO19391	Bevacizumab	Higher risk for grade 3 hypertension (7%) than in younger patients (4%)		Pivot et al. (2009) [20]
E2100	Bevacizumab + paclitaxel	<ul style="list-style-type: none"> ● Grade 3–4 hypertension (14.8%) ● Infection (9.3%) 	Take into account comorbidities and associated risk factors	Gray et al. (2009) [26] Miller et al. (2007) [24]
LEAP	Lapatinib	<ul style="list-style-type: none"> ● Gastrointestinal ● Dermatologic ● Impairment of the left ventricle ejection function (0.5%) 		Capri et al. (2010) [30]
	Lapatinib + letrozole	<ul style="list-style-type: none"> ● Diarrhea ● Rash 	<ul style="list-style-type: none"> ● Recommended in coexpression of HER-2 and HR ● Longer progression-free survival time (8.2 mos, versus 3.0 mos for letrozole alone) 	Johnston et al. (2009) [49]
	Neratinib	No cardiologic side effects		Burstein et al. (2010) [57]
Abbreviations: AVADO, Avastin® and Docetaxel; HERA, Herceptin® Adjuvant; HER-2, human epidermal growth factor receptor 2; HR, hormone receptor; LEAP, Lapatinib Expanded Access Program; NSABP, National Surgical Adjuvant Breast and Bowel Project; TanDEM, Trastuzumab and Anastrozole in metastatic breast cancer.				

older patients to anthracyclines and suggests that appropriate identification and exclusion of patients at high cardiac

risk should increase their relative survival rate. For this purpose, the implementation of key exclusion criteria, such as

a history of chronic heart failure and prior exposure to anthracyclines, should be conducted.

The use of anthracycline-based chemotherapy illustrates many of the dilemmas facing elderly cancer patients. The risk for cardiotoxicity with conventional anthracyclines is increased by existing or a history of heart failure or cardiac dysfunction; hypertension, diabetes, and coronary artery disease; older age (independent of comorbidities and performance status); prior treatment with anthracyclines; higher cumulative doses of anthracyclines; and a short infusion time. Cumulative and irreversible cardiotoxicity is likely to be greater in this population than among younger patients; as a consequence, it is important to perform an effective screening for risk factors prior to treatment initiation, and to conduct rigorous monitoring of cardiac function during treatment. The use of liposomal anthracycline formulations, prolonging the infusion time for conventional anthracyclines, and cardioprotective measures should be considered. However, care should be taken to ensure that reducing cardiotoxicity does not compromise efficacy [56].

Future recommendations for the treatment of elderly women with breast cancer should include a multidisciplinary approach before any treatment with either anti-HER-2 therapy or bevacizumab. A global geriatric assessment conducted by trained physicians is strongly recommended to evaluate the appropriateness of treatments.

ACKNOWLEDGMENTS

The authors have received a support grant from AVEC. The authors wish to thank A.P.M.W. for help with the manuscript.

AUTHOR CONTRIBUTIONS

Conception/Design: Jean-Philippe Spano, Claire Falandry, Gilles Freyer, Pascal Chaibi
Provision of study material or patients: Jean-Philippe Spano, Claire Falandry, Gilles Freyer, Pascal Chaibi
Collection and/or assembly of data: Jean-Philippe Spano, Claire Falandry, Gilles Freyer, Pascal Chaibi
Data analysis and interpretation: Jean-Philippe Spano, Claire Falandry, Gilles Freyer, Pascal Chaibi
Manuscript writing: Jean-Philippe Spano, Claire Falandry, Gilles Freyer, Pascal Chaibi
Final approval of manuscript: Jean-Philippe Spano, Claire Falandry, Gilles Freyer, Pascal Chaibi

REFERENCES

- 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;8:1101–1115.
- Pal SK, Katheria V, Hurria A. Evaluating the older patient with cancer: Understanding frailty and the geriatric assessment. *CA Cancer J Clin* 2010;60:120–132.
- Balducci L, Extermann M. A practical approach to the older patient with cancer. *Curr Probl Cancer* 2001;25:6–76.
- Hamerman D. Toward an understanding of frailty. *Ann Intern Med* 1999;130:945–950.
- Crivellari D, Spazzapan S, Puglisi F et al. Hormone therapy in elderly breast cancer patients with comorbidities. *Crit Rev Oncol Hematol* 2010;73:92–98.
- Pierga JY, Girre V, Laurence V et al. Characteristics and outcome of 1755 operable breast cancers in women over 70 years of age. *Breast* 2004;13:369–375.
- Satariano WA, Ragland DR. The effect of comorbidity on 3-year survival of women with primary breast cancer. *Ann Intern Med* 1994;120:104–110.
- Cutuli B, De Lafontan B, Vitali E et al. Breast conserving treatment (BCT) for stage I-II breast cancer in elderly women: Analysis of 927 cases. *Crit Rev Oncol Hematol* 2009;71:79–88.
- Louwman WJ, Janssen-Heijnen ML, Houterman S et al. Less extensive treatment and inferior prognosis for breast cancer patient with comorbidity: A population-based study. *Eur J Cancer* 2005;41:779–785.
- Molino A, Giovannini M, Auriemma A et al. Pathological, biological and clinical characteristics, and surgical management, of elderly women with breast cancer. *Crit Rev Oncol Hematol* 2006;59:226–233.
- Durbecq V, Ameye L, Veys I et al. A significant proportion of elderly patients develop hormone-dependant “luminal-B” tumours associated with aggressive characteristics. *Crit Rev Oncol Hematol* 2008;67:80–92.
- Schonberg MA, Marcantonio ER, Li D et al. Breast cancer among the oldest old: Tumor characteristics, treatment choices, and survival. *J Clin Oncol* 2010;28:2038–2045.
- Aapro M, Monfardini S, Jirillo A et al. Management of primary and advanced breast cancer in older unfit patients (medical treatment). *Cancer Treat Rev* 2009;35:503–508.
- Tse GM, Tan PH, Lau KM et al. Breast cancer in the elderly: A histological assessment. *Histopathology* 2009;55:441–451.
- Okunade G, Green AR, Ying M et al. Biological profile of oestrogen receptor positive primary breast cancers in the elderly and response to primary endocrine therapy. *Crit Rev Oncol Hematol* 2009;72:76–82.
- Barthélémy P, Heitz D, Mathelin C et al. Adjuvant chemotherapy in elderly patients with early breast cancer. Impact of age and comprehensive geriatric assessment on tumor board proposals. *Crit Rev Oncol Hematol* 2009;72:S18.
- Hutchins LF, Unger JM, Crowley JJ et al. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med* 1999;341:2061–2067.
- Piccart-Gebhart MJ, Procter M, Leyland-Jones B et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005;353:1659–1672.
- Romond EH, Perez EA, Bryant J et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005;353:1673–1684.
- Pivot X, Villanueva C, Bazan F et al. How safe is bevacizumab for elderly patients? *Crit Rev Oncol Hematol* 2009;18:S10.
- Slamon DJ, Leyland-Jones B, Shak S et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that over-expresses HER2. *N Engl J Med* 2001;344:783–792.
- Tu CM, Chu KM, Yang SP et al. Trastuzumab (Herceptin)-associated cardiomyopathy presented as new onset of complete left bundle-branch block mimicking acute coronary syndrome: A case report and literature review. *Am J Emerg Med* 2009;27:903.e1–e3.

- 23 Al-Dasooqi N, Bowen JM, Gibson RJ et al. Trastuzumab induces gastrointestinal side effects in HER2-overexpressing breast cancer patients. *Invest New Drugs* 2009;27:173–178.
- 24 Miller K, Wang M, Gralow J et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med* 2007;357:2666–2676.
- 25 Valachis A, Polyzos NP, Patsopoulos NA et al. Bevacizumab in metastatic breast cancer: A meta-analysis of randomized controlled trials. *Breast Cancer Res Treat* 2010;122:1–7.
- 26 Gray R, Bhattacharya S, Bowden C et al. Independent review of E2100: A phase III trial of bevacizumab plus paclitaxel versus paclitaxel in women with metastatic breast cancer. *J Clin Oncol* 2009;27:4966–4972.
- 27 Scappaticci FA, Skillings JR, Holden SN et al. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. *J Natl Cancer Inst* 2007;99:1232–1239.
- 28 Randall LM, Monk BJ. Bevacizumab toxicities and their management in ovarian cancer. *Gynecol Oncol* 2010;117:497–504.
- 29 Geyer CE, Forster J, Lindquist D et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 2006;355:2733–2743.
- 30 Capri G, Chang J, Chen SC et al. An open-label expanded access study of lapatinib and capecitabine in patients with HER2-overexpressing locally advanced or metastatic breast cancer. *Ann Oncol* 2010;21:474–480.
- 31 Britten CD, Finn RS, Bosserman LD et al. A phase I/II trial of trastuzumab plus erlotinib in metastatic HER2-positive breast cancer: A dual ErbB targeted approach. *Clin Breast Cancer* 2009;9:16–22.
- 32 Baselga J, Gelmon KA, Verma S et al. Phase II trial of pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer that progressed during prior trastuzumab therapy. *J Clin Oncol* 2010;28:1138–1144.
- 33 Krop IE, Beeram M, Modi S et al. Phase I study of trastuzumab-DM1, an HER2 antibody-drug conjugate, given every 3 weeks to patients with HER2-positive metastatic breast cancer. *J Clin Oncol* 2010;28:2698–2704.
- 34 Burris HA 3rd, Rugo HS, Vukelja SJ et al. Phase II study of the antibody drug conjugate trastuzumab-DM1 for the treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer after prior HER2-directed therapy. *J Clin Oncol* 2011;29:398–405.
- 35 Serrano C, Cortés J, Russillo M et al. Trastuzumab-related cardiotoxicity in the elderly: Which role for cardiovascular risk factors? *Eur J Cancer Suppl* 2009;7:216.
- 36 Baselga J, Perez EA, Pienkowski T et al. Adjuvant trastuzumab: A milestone in the treatment of HER-2-positive early breast cancer. *The Oncologist* 2006;11(suppl 1):4–12.
- 37 Procter M, Suter TM, de Azambuja E et al. Longer-term assessment of trastuzumab-related cardiac adverse events in the Herceptin Adjuvant (HERA) trial. *J Clin Oncol* 2010;28:3422–3428.
- 38 Brain EGC. Anthracyclines in elderly cancer patient: A SIOG expert position paper. *Crit Rev Oncol Hematol* 2009;72:S13.
- 39 Baselga J, Bradbury I, Eidtmann H et al. First results of the NeoALTTO trial (BIG 01-06 / EGF 106903): A phase III, randomized, open label, neo-adjuvant study of lapatinib, trastuzumab, and their combination plus paclitaxel in women with HER2-positive primary breast cancer [abstract S3-3]. Presented at the 33rd Annual San Antonio Breast Cancer Symposium, San Antonio, Texas, December 8–12, 2010.
- 40 Jones S, Holmes FA, O'Shaughnessy J et al. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology Research Trial 9735. *J Clin Oncol* 2009;27:1177–1183.
- 41 Singletary SE, Robb GL, Hortobagyi GN. *Advanced Therapy of Breast Disease*, Second Edition. Hamilton, Canada: BC Decker, 2004:1–22.
- 42 Valero V, Forbes J, Pegram MD et al. Multicenter phase III randomized trial comparing docetaxel and trastuzumab with docetaxel, carboplatin, and trastuzumab as first-line chemotherapy for patients with HER2-gene-amplified metastatic breast cancer (BCIRG 007 Study): Two highly active therapeutic regimens. *J Clin Oncol* 2011;29:149–156.
- 43 Pierga JY, Delaloge S, Espié M et al. A multicenter randomized phase II study of sequential epirubicin/cyclophosphamide followed by docetaxel with or without celecoxib or trastuzumab according to HER2 status, as primary chemotherapy for localized invasive breast cancer patients. *Breast Cancer Res Treat* 2010;122:429–437.
- 44 Glissmeyer M. Reviewing prognostic factors in breast cancer management. *JAAPA* 2007;20:42–46.
- 45 McKeage K, Perry CM. Trastuzumab: A review of its use in the treatment of metastatic breast cancer overexpressing HER2. *Drugs* 2002;62:209–243.
- 46 Perez EA, Rodeheffer R. Clinical cardiac tolerability of trastuzumab. *J Clin Oncol* 2004;22:322–329.
- 47 Kaufman B, Mackey JR, Clemens MR et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: Results from the randomized phase III TAnDEM study. *J Clin Oncol* 2009;27:5529–5537.
- 48 Perez EA, Koehler M, Byrne J et al. Cardiac safety of lapatinib: Pooled analysis of 3689 patients enrolled in clinical trials. *Mayo Clin Proc* 2008;83:679–686.
- 49 Johnston S, Pippin J Jr, Pivot X et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. *J Clin Oncol* 2009;27:5538–5546.
- 50 Moreira C, Kaklamani V. Lapatinib and breast cancer: Current indications and outlook for the future. *Expert Rev Anticancer Ther* 2010;10:1171–1182.
- 51 Petrelli F, Barni S. Bevacizumab in advanced breast cancer: An opportunity as second-line therapy? *Med Oncol* 2010 Dec 14 [Epub ahead of print]. doi: 10.1007/s12032-010-9773-z.
- 52 Gligorov J, Namer M. Recommendations pour la pratique clinique, Nice, Saint-Paul-de-Vence: et de trois! *Oncologie* 2009;11:495–496.
- 53 Bennett CL, Silver SM, Djulbegovic B et al. Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. *JAMA* 2008;299:914–924.
- 54 Costa RB, Kurra G, Greenberg L et al. Efficacy and cardiac safety of adjuvant trastuzumab-based chemotherapy regimens for HER2-positive early breast cancer. *Ann Oncol* 2010;21:2153–2160.
- 55 Lee CM, Szabo A, Schrieve DC et al. Frequency and effect of adjuvant radiation therapy among women with stage I endometrial adenocarcinoma. *JAMA* 2006;295:389–397.
- 56 Aapro M, Bernard-Marty C, Brain EG et al. Anthracycline cardiotoxicity in the elderly cancer patient: A SIOG expert position paper. *Ann Oncol* 2011;22:257–267.
- 57 Burstein HJ, Sun Y, Dirix LY et al. Neratinib, an irreversible ErbB receptor tyrosine kinase inhibitor, in patients with advanced ErbB2-positive breast cancer. *J Clin Oncol* 2010;28:1301–1307.