

REVIEW ARTICLE

Treatment of breast cancer in older women

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Abstract

Background. Breast carcinoma management in the elderly often differs from the management in younger women and there is considerable controversy about what constitutes appropriate cancer care for older women. This controversy is reflected in the persistence of age-dependent variations in care over time, with older women being less likely to receive definitive care for breast cancer. There has been a significant increase in the last years in the number of studies conducted in older patients with breast cancer. Although available age-specific clinical trials data demonstrate that treatment efficacy is not modified by age, this evidence is limited by the lack of inclusion of substantial numbers of older women, particularly those of advanced age and those with comorbidities. **Method.** The literature-based evidence of the last 10 years was extensively reviewed on the main issues concerning the treatment of breast cancer in older women. **Results.** Surgical treatment in older patients has evolved from avoidance to mastectomy to breast-conserving surgery, similarly to younger patients. Given its negative effect on the quality of life, in the last few years the role of adjuvant radiotherapy has been questioned in elderly patients with breast cancer. Adjuvant chemotherapy benefit in older patients applies mainly to Estrogen-receptor-negative patients, while in Estrogen-receptor-positive patients a major role is played by endocrine treatment. New “elderly-friendly” drugs, that can help clinicians to reduce toxicity, are now available for breast cancer.

Breast cancer represents the most common malignant disease among women in Western Countries and aging remains the largest single risk factors for the development of new breast carcinoma [1]. Approximately 50% of breast carcinomas occur in women ≥ 65 years and $>30\%$ of breast carcinomas occurs among women >70 years [2].

Treatment of breast cancer in older patients has been influenced for years by a number of misconceptions [3]. Despite evidence to the contrary, there is a belief that breast carcinoma in the elderly is less aggressive than breast carcinoma in younger women. For this reason, along with the higher incidence of comorbidities, breast carcinoma management in the elderly often differs from the management in younger women, with older women being less likely to receive definitive care for breast cancer [4]. Women aged 70 years or older are also less commonly included in randomized clinical trials, making the therapeutic impact of new

approaches difficult to assess in this population. Moreover, published data are controversial due to biases both in the conduct and interpretation of trial results. For instance, it should be taken into account that in the literature the cut-off age varies throughout the different studies and has increased with time, in the majority of reports, up to 70 years.

Perceived barriers to accrual of older patients include the presence of comorbid conditions that may affect response to treatment, the likelihood of poor compliance, treatment toxicity and exclusion due to eligibility criteria [5].

As a result, there is considerable controversy about what constitutes appropriate cancer care for older women with newly diagnosed breast cancer [6,7]. Furthermore, treatment decisions must be based not only on disease control and survival, but also on patient's unique circumstances, goals and expectations. For the elderly patients, functional

capacity and quality of life may exert additional impact on decision-making.

Oncologists have learned from geriatricians instruments such as the comprehensive geriatric assessment (CGA) can define those patients who are more suitable for aggressive chemotherapy or, on the contrary, palliative treatment. A CGA includes an evaluation of an older individual's functional status, comorbid medical conditions, cognition, nutritional status, psychological state, and social support, and a review of the patient's medications. Moreover, the use of a CGA prior to the treatment of elderly patients would enable a detailed assessment of their suitability for treatment and highlight any areas of concern that may require close attention before and during treatment and also predict morbidity and mortality.

We conducted an extensive review of the literature-based evidence concerning the treatment of breast cancer in older women.

Research methods

A literature search was performed for English-language literature from 1996 to 2006 on MEDLINE and Cochrane, using the terms *breast cancer*, *elderly*, *older patients*, *treatment*, and, according to the different sections, *chemotherapy*, *endocrine therapy*, *surgery* and *radiotherapy*. Relevant references of literature were manually reviewed for additional material. Further information was obtained in oral and abstract form at the 2005 and 2006 American Society of Clinical Oncology (ASCO) meetings, the 2005 San Antonio International Breast Cancer Meeting, the 2005 and 2006 American Society for Therapeutic Radiology and Oncology (ASTRO) meetings. Published guidelines from the National Comprehensive Cancer Network (NCCN), the ASCO and the 2005 St. Gallen expert consensus meeting were also reviewed.

Results

Early disease

Surgery. The principal aims of breast cancer surgery are i) to maximize local control; ii) to achieve cure when possible; iii) to stage disease and determine likely prognosis; iv) to cause least possible alteration to body image.

One of the main arguments used to justify under-treatment of cancer in the elderly is that they will have concomitant comorbidities which will lead to their death before cancer becomes problematic. Available evidence indicates that there is little, if any, relationship between comorbidity and adequacy of

surgery [8–12]. Therefore, surgical approaches to elderly and to younger patients should be similar, in keeping the principle of ensuring that each individual is offered an equal opportunity to receive appropriate treatment. For instance, if older patients are suitable for breast conservation surgery, they should be offered this treatment modality similarly to younger patients.

Avoidance of surgery. A series of European trials, conducted in the 1980s and 1990s compared tamoxifen alone with some form of surgery [13–16] (Table I). The St George's Hospital trial compared wide excision or total mastectomy with tamoxifen alone. Local relapse or progression occurred in 56% of the tamoxifen group and 44% of the surgery group. Mortality rates were similar in both arms.

In another trial conducted in Nottingham, patients were treated by either tamoxifen (40 mg daily) or by wedge mastectomy. No differences in terms of overall survival but significantly better local control in the surgery group were shown.

In the Cancer Research Campaign (CRC) Trial, both arms received tamoxifen. Significantly more of the tamoxifen only group needed a change of treatment (46% versus 21%). Furthermore 28% of the tamoxifen group had died compared with 21% of the surgery and tamoxifen group and this difference just reached statistical significance.

The Group for Research on Endocrine Treatment in the Elderly conducted the GRETA trial in which 473 patients aged >70 years were randomized to

Table I. Randomized trials of surgical treatment for breast cancer in older women.

Trial	Follow-up	Surgery arm	Tamoxifen arm
St George's Hospital	6 years	n = 100	n = 100
Local relapse/progression		44%	56%
Breast cancer deaths		15%	17%
Other deaths		13%	16%
Nottingham City Hospital	12 years	n = 65	n = 66
Local relapse/progression		38%	81%
Breast cancer deaths		22	20
Other deaths		24	25
CRC Elderly Trial	12.3 years	n = 225	n = 230
Local relapse/progression		21%	46%
Breast cancer deaths		19%	30%
Other deaths		51%	52%
GRETA	6.75 years	n = 239	n = 235
Local relapse/progression		11%	40%
Breast cancer deaths		23%	24%
Other deaths		21%	37%
EORTC 10851	10 years	82	82
Local relapse/progression		9%	57%
Breast cancer deaths		23%	28%
Other deaths		50%	33%

either a loading dose of tamoxifen (160 mg) followed by 20 mg daily or to surgery plus tamoxifen. Local progression occurred in 11% of the surgery group compared with 40% of the tamoxifen alone arm [17].

In the European Organization for Research and Treatment of Cancer (EORTC) trial 10851, patients with operable disease were randomized to either tamoxifen alone or modified radical mastectomy [13]. Tamoxifen alone led to an unacceptably high rate of local progression or relapse.

Hind et al. conducted a Cochrane review of surgery versus endocrine therapy for women aged over 70 and concluded that primary endocrine therapy alone should only be offered to patients with endocrine responsive tumors unfit for or refusing surgery [18].

Mastectomy and wide excision of tumor. In younger women the indications for mastectomy are a large primary tumor in a patient who does not wish to have neoadjuvant therapy, multicentric invasive disease or ductal carcinoma in situ (DCIS), tumors close to the nipple-areola complex and recurrence after breast conserving therapy. The same is true for older women but, because they are more likely to have ER tumors, the option of neoadjuvant endocrine therapy with tamoxifen or an aromatase inhibitor (AI) is more likely to be successful.

Regarding breast conserving surgery (BCS), Gori et al. conducted a trial in which 121 breast cancer patients with operable disease and clinically negative axillae were randomized to wide excision plus tamoxifen or mastectomy plus tamoxifen [19]. After 5 years, the overall survival of the two groups was similar. In the EORTC 10850 trial, patients aged >70 were randomized to wide excision plus tamoxifen or mastectomy without tamoxifen [20]. After 10 years of follow-up, local relapse had occurred in 16% of the mastectomy group and 26% of the wide excision group. Overall survival was similar. It is likely that selection of patients with endocrine responsive tumors will lead to more acceptable local control rates after wide excision alone.

Treatment of the axilla: Sentinel node biopsy and avoidance of surgery. It is now generally accepted that in terms of everyday practice, the major determinant of prognosis in operable breast cancer is the status of the axillary lymph nodes, not just the presence but the extent of metastatic disease therein. Moreover, for the involved axilla, clearance may have a therapeutic impact in addition to staging of disease. All the trials included in a meta-analysis [21] showed a survival benefit from axillary clearance of 4–16%. However, two of the studies had a cut-off point of 70 years.

To reduce the morbidity associated with an axillary clearance, sentinel node biopsy (SNB) has

been widely taken up as the staging procedure for the axilla. DiFronzo et al. performed intraoperative lymphatic mapping on 86 breast cancer patients aged >70 years [22]. No sentinel node was found in 15% and these cases had axillary lymph node dissection (ALND). Axillary metastases were found in 43%. As a result of SNB with or without ALND, there was a change in treatment for 11 patients.

McMahon et al. reported 261 SNBs in older women with a 97% identification rate [23]. SNB metastases were detected by H&E in 13% and by immunohistochemistry in a further 5%. Chemotherapy was given to 24% of SNB-positive cases and 3% of SNB-negative patients. What has yet to be demonstrated is that these changes in therapy are associated with an improvement in outcome.

Two important randomized trials explored avoidance of axillary surgery in selected groups of patients. In the first one Martelli et al. [24] concluded that axillary clearance could be avoided as primary treatment for women aged 65–80 who had early (T1) breast cancer with clinically negative nodes and should be reserved for those patients who developed axillary relapse. In the International Breast Cancer Study Group (IBCSG) Trial 10–93 [25] it was suggested that axillary clearance can be avoided in older women who are N₀ with estrogen receptor (ER)-positive cancers.

Breast reconstruction. August et al. reported a series of 18 older patients who underwent postmastectomy reconstruction [26] and later Girotto gave results from a series of 28 women aged >65 years [27]. When quality of life was examined in those who had undergone reconstruction and compared with age-matched mastectomized controls, the former group had better outcomes in those subscales dependent upon mental health.

Not all older women want reconstruction [28,29]. The common reasons for not wanting further surgery were fear of complications, perception of being too old for the procedure and fear concerning the effect of reconstruction on risk of relapse.

As there has been increasing acceptance by surgeons that reconstruction is feasible in older women so the emphasis has moved to selection of patients and procedures [30–32].

Patient choice and body image. When patients are asked whether they feel they had a choice of treatment and their satisfaction with that treatment, those who feel that their surgeons discussed more treatment options are twice as likely to report being given a choice and have a 33% increase in likelihood of having breast conserving surgery [33].

Within EORTC trial 10850, comparing mastectomy with wide excision and tamoxifen in women aged >70, an embedded quality of life (QOL)

study was conducted [34]. In terms of fatigue, emotional functioning and fear of relapse there were no differences between the two randomized groups. Patients who underwent mastectomy, however, had more arm problems and worsening of body image compared with those treated by wide excision and tamoxifen.

No significant differences by treatment group were observed in a telephone survey on Medicare beneficiaries between 3 and 5 years after breast cancer treatment with regard to physical or emotional function [35]. Among those women who had an axillary clearance there was a 4-fold increase in arm problems and this impacted negatively on all other domains, including satisfaction with care, pain and physical and emotional function.

Figueiredo et al. examined the relationship between treatment received, treatment choice and post-operative body image. For over 30% of the women body image was an important factor in terms of the decision they made and those who had BCS had a significantly better body image compared with those who had a mastectomy. The group who fared worst with body image were those who had a mastectomy but would have preferred breast conservation and this was reflected in the mental health state 2 years after surgery [36].

Radiotherapy. Multiple trials of BCS for breast cancer have shown that postoperative irradiation decreases the rate of ipsilateral recurrence but offers no survival benefit [37,38]. However, the high rate of recurrence with surgery alone (10 to 40%) has suggested that the only two appropriate treatments are modified radical mastectomy and BCS plus adjuvant radiotherapy.

Risk of local recurrence is lower in older women, particularly those receiving adjuvant tamoxifen or chemotherapy [39]. For these reasons, the Cancer and Leukemia Group B (CALGB) assessed in a randomized trial the benefit of tamoxifen alone or with radiotherapy in women ≥ 70 years who had small (T1) lymph node-negative, ER-positive breast cancer [40]. This trial found that the rate of recurrence at 5 years was reduced to 1% with combined radiotherapy and tamoxifen compared with 4% with tamoxifen alone. No differences in rates of subsequent mastectomy for treatment of recurrences, survival rate or rate of freedom from distant metastases were found. In this study, though, breast pain and skin fibrosis or retraction were worse in women who had undergone breast irradiation and women who received irradiation reported significantly worse shoulder and arm stiffness.

Given the small absolute benefit of radiotherapy, coupled with its cost and morbidity, new clinical guidelines have included as an option the omission of breast radiation therapy for women meeting the criteria of the CALGB study [41]. On the other hand, the CALGB was a randomized trial, and selection bias raises concerns that a clinical trial result cannot be generalized to the community practice of older women [39].

An observational study was performed [42], using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database to assess the risk of local recurrence among 8 724 women ≥ 70 years who also matched the CALGB trial inclusion criteria. Local recurrences were reduced by 4% at 5 years and by 5.7% at 8 years. Hence, women who lived longer were more likely to benefit from radiation therapy.

In the general population of patients aged ≥ 70 years with small, ER-positive (or of unknown hormonal status) lymph node-negative breast cancer, radiotherapy after BCS is associated with a lower risk of a second ipsilateral breast cancer and subsequent mastectomy. Patients with lobular histology and those aged 70–79 years with minimal comorbidity, were more likely to benefit from radiotherapy. In contrast, patients of advanced age or with moderate to severe comorbid illness were less likely to experience the benefit associated with radiotherapy. For women who do not meet the strict age, size, and hormone receptor criteria outlined for the CALGB trial, the absolute benefit of radiotherapy is substantial, and radiotherapy should remain the standard of care.

Without consistent data from adequately powered prospective trials of older subjects, the lack of consensus in breast-conserving management in older populations is reflected by numerous small retrospective series reporting diverse treatment approaches and results. Some studies suggest that among older women, clinical outcomes are not compromised by avoidance of radiotherapy after BCS [43–45]. In contrast, others report substantial rates of local relapse, 20–40%, among elderly women not given radiotherapy [46,47].

With the aim of identifying a subgroup of patients with a low risk of recurrence after BCS, in order to avoid radiotherapy, a review was performed by an Italian group [48]. In this study, for those aged ≤ 75 years a benefit in local control was observed in patients with T1/T2 tumors given radiotherapy, but in those ≥ 75 years radiotherapy treatment did not significantly improve disease free survival. This suggested that radiotherapy could be withheld in patients ≥ 75 years who had completely excised grade I tumors.

In women younger than 70 years with primary tumors >5 cm or ≥ 4 positive axillary nodes, post-mastectomy radiotherapy has been shown to consistently reduce the risk of locoregional recurrence by about two-thirds in prospective randomized trials [37,49], and recent guidelines support the use of post-mastectomy radiotherapy in this setting [50]. A retrospective analysis suggested that women ≥ 70 years with similar high-risk factors also significantly benefit from adjuvant radiotherapy after mastectomy [51].

Very recently, in a study of almost 20 000 older women, Punglia and coworkers [52] analyzed the changing temporal patterns in use of post-mastectomy irradiation as the benefit of radiation therapy in this setting became evident. During the entire period studied, 2160 (11%) patients treated with mastectomy received post-mastectomy radiation therapy and this approach significantly increased in women diagnosed in 1996–1999 period as compared to those diagnosed in 1991.

In conclusion, while ongoing trials are trying to identify which elderly patients do not benefit from radiotherapy both after conservative surgery and mastectomy, likewise the low risk patients, nowadays adjuvant RT should be routinely offered to elderly patients with breast cancer. In this regard, novel adjuvant RT strategies, such as accelerated partial breast irradiation or intraoperative approaches, may become an extremely appealing option for selected elderly patients.

Endocrine therapy.

Adjuvant endocrine therapy. Most elderly patients, presenting with larger tumors and nodal involvement at diagnosis, are good candidate for adjuvant endocrine therapy, since the percentage of endocrine responsive tumors increases with age, up to 90% in the oldest patients [43,53].

In postmenopausal women, adjuvant tamoxifen for 5 years is known to almost halve the annual relative risk of breast cancer recurrence and reduce the mortality by a third by being allocated active treatment. The benefit, greater in early years and persistent throughout the first 15 years, is similar across age groups, particularly for patients ≥ 70 years [54]. A 0.2% excess mortality for endometrial cancer or thromboembolic events has been reported with 5 years adjuvant tamoxifen, with no net excess of other cancers, or a significant increase in stroke deaths. Among older tamoxifen users, however, the risk of death from thromboembolic events significantly increases, from 1.5 in patients aged 50 to 8.8 and 17.5 respectively, in those aged 70 and 80 years [55].

Recently, AIs used as initial adjuvant therapy, or sequentially after 2 to 5 years of tamoxifen, have shown to further reduce the relative risk of recurrence by 13–43% and of contralateral breast cancer by 39–56%, with an absolute 2.4–6% gain in disease-free survival (DFS). Some survival benefits also have been reported in limited subsets, but data are largely immature [56–60]. Toxicity was significantly lower compared to tamoxifen, except for hot flashes, musculoskeletal complaints/arthritis and a small but significant increased risk of osteoporosis and fractures [61]. All AIs induce bone resorption. However, Bone Mineral Density testing and effective treatment interventions, according to ASCO 2003 guidelines, may minimize the risk of fractures, particularly in elderly women [62,63]. Finally, negative effects of AIs on cardiovascular system and lipid metabolism have not been conclusively demonstrated, and no significant differences in overall quality of life were observed [61,64,65].

AIs therefore, may offer an appropriate adjuvant endocrine option even to elderly patients. Careful evaluation of concomitant comorbidities and the different spectrum of toxicity of tamoxifen versus AIs (cardiovascular events, lipid metabolism, pre-existent osteoporosis, cognitive functions) has also to be taken into account when recommending adjuvant endocrine therapy in the elderly population.

Neoadjuvant endocrine therapy. In elderly patients with locally advanced breast cancer, neoadjuvant tamoxifen appeared effective (47–67% objective responses) (OR) and well tolerated in early uncontrolled studies, but objective response rates (ORRs) resulted substantially decreased ($\sim 36\%$) in randomized trials [66,67]. Similar ORRs (36–39%) but greater probability of BCS (43–46%) were observed in favor of Anastrozole, compared to Tamoxifen, in two large randomized trials [68,69]. Letrozole gave significantly higher ORRs compared with tamoxifen and a greater likelihood of enabling BCS [70]. A superior activity versus Tamoxifen was observed with Letrozole in patients with weak ER expression and with Letrozole and Anastrozole in HER2 overexpressing tumors [68,70].

In early breast cancer, a recent meta-analysis of neoadjuvant tamoxifen trials in patients aged ≥ 70 years [18], has shown similar overall survival but higher progression-free survival for surgery alone, or followed by adjuvant tamoxifen, compared to tamoxifen alone. It appears therefore that neoadjuvant tamoxifen should only be offered to elderly women with endocrine responsive tumors, who are unfit for or refuse surgery. Adequate trials are still needed for neoadjuvant AIs in this elderly population with early breast cancer [18,71].

Chemotherapy.

Adjuvant chemotherapy. Adjuvant chemotherapy was very rarely used in elderly patients in the past [12,72–76], but there is a widespread feeling that a new era is now opening.

In the last overview of randomized adjuvant therapy trials in early breast cancer [54], a lesser absolute benefit from chemotherapy was observed with increasing age, even though only about 3% were 70 years or older.

The survival benefit from adjuvant chemotherapy in endocrine unresponsive older patients only was recently examined by the Memorial Sloan-Kettering Cancer Center Group [77] using SEER data. There were 1711 women with ER-negative stage I to III breast cancer treated from 1992 to 1999. A dramatically significant reduction in the use of chemotherapy with increasing age was seen. The survival benefit seen in the entire cohort was largely derived from that in the node-positive disease. These data are in agreement with those of Giordano et al. [78] who examined outcome, in the SEER database, for all patients older than 65 years with stage I to III breast cancer, (both ER-positive and ER-negative). There was a significant reduction in mortality among older women with ER-negative and node-positive disease. Furthermore, the use of adjuvant chemotherapy more than doubled during the 1990s, from 7.4% in 1991 to 16.3% in 1999.

The optimal chemotherapy regimens, doses and schedules for adjuvant treatment of elderly patients have not yet been defined, while concern is increasing regarding the toxicity associated with cytotoxic regimens in this patient population. In a recent paper, the CALGB analyzed [79], the differential efficacy and tolerability of four randomized clinical adjuvant trials with different chemotherapy regimens. Older patients were found to have a worse overall survival compared with younger patients mainly due to competing causes of death, while an increase in treatment-related mortality was also reported in the very old. Furthermore, in the same review, DFS, overall survival and treatment-related mortality were analyzed among three different age groups (50 years or younger, 51–64 years, and 65 years or older). These were all node positive breast cancer patients treated during the period 1975–1999. Of 6 487 women, only 8% were ≥ 65 years and 2% were ≥ 70 . Hence, their conclusions that older and younger women derived similar reductions in breast cancer mortality and recurrence from chemotherapy regimens must be taken with caution.

Non-anthracycline-containing regimens were thought to be preferable because of the fear of cardiac toxicity in older patients, but regimens such as CMF showed no significant advantage over

tamoxifen in different trials involving older women [80,81]. The IBCSG [81] examined the toxicity encountered in the elderly subgroup of patients treated with three cycles of classic CMF planned at full doses and found a significant relationship between older age and increased incidence of grade 3 toxicity from adjuvant chemotherapy, with no significant difference in survival between the treatment groups. Similar findings of a relevant burden of toxicity with six cycles of CMF, were recently reported by another group in a single institution [82] suggesting that less toxic treatments should be studied for elderly patients.

Doxorubicin-based chemotherapy seems to be more effective as was reported in the NSABP B-16 trial [83] with a short course (four cycles) of doxorubicin and cyclophosphamide combined with tamoxifen being superior to tamoxifen alone. The International Collaborative Cancer Group reported a benefit in terms of DFS with Epirubicin in 604 patients [84]. This was confirmed by a recent French study on 338 elderly women with node-positive disease showing a significant DFS benefit with weekly Epirubicin and tamoxifen over tamoxifen alone [85]. Unfortunately, this trial is underpowered to draw definite conclusions on the advantage of anthracyclines, but represents a further suggestion in this direction.

An observational study recently reported at the last ASCO meeting [86] showed that even if women aged 66–70 treated with anthracycline-containing regimens tended to be healthier, rates of congestive heart failure (CHF) were significantly higher than with other non-anthracycline containing regimens and, more importantly, the difference continued to increase through 10 years of follow-up.

An NCI-supported randomized trial comparing standard adjuvant chemotherapy (CMF or AC) with the oral agent capecitabine is ongoing for women ≥ 65 years with high-risk node-negative and node-positive breast cancer and other trials started recently in German, British [87] and IBCSG groups (ibcsg32-05_casa@ibcsg.org). This last trial was planned only for patients with ER-negative early breast cancer, in order to determine whether chemotherapy (liposomal doxorubicin) has a positive impact, without the confounding role of hormonal treatments.

In conclusion, more studies on this issue are needed, in particular, limiting the enrollment to women who are likely to experience a measurable benefit, exploring new and less toxic forms of chemotherapy, protecting older individuals from the toxicity of chemotherapy, exploring a more comprehensive assessment of quality of life to establish whether reduction of tumor recurrence is a real benefit.

Advanced disease

Endocrine therapy. Endocrine therapy, aiming to palliate symptoms and preserve quality of life, is the treatment of choice for patients with endocrine responsive disease of all age groups, because of its favorable toxicity profile. While Tamoxifen may obtain 20–30% ORRs, 50–60% of clinical benefit, 6–8 months of TTP, all other Selective Estrogen Receptor Modulators (SERMs) are less effective and cross-resistant [53]. AIs appeared equal to or more effective and better tolerated than tamoxifen in several randomized trials, even in older patients [88], and are widely accepted as first line therapy [82–92]. (Table II). Recently, however, a pooled analysis of six phase III AIs trials, has shown a significant heterogeneity among studies, suggesting caution in deriving summary estimates in favor of AIs [93].

Patients progressing after adjuvant and first line endocrine therapy may benefit from the pure anti-estrogen Fulvestrant, which is well tolerated and has no agonist effects. Fulvestrant was as effective as Anastrozole in tamoxifen-resistant postmenopausal patients and survival data compared well with the AIs [94,95]. However, when tested as first line treatment in the overall population (ER-positive and unknown receptor tumors), Fulvestrant showed inferior efficacy compared with tamoxifen, except in the subgroup of patients with ER-positive tumors [96].

Patients responding to first-line therapies retain sensitivity to subsequent endocrine treatment, including progestins, with similar ranges of efficacy [53,97]. In elderly patients however, different comorbidities may limit the efficacy of endocrine therapies, so the risk of adverse events should first be weighed against the benefits of treatment.

Finally, the improved understanding of the mechanisms of hormonal resistance and of cross-talk among hormonal and growth factor receptors, has provided the rationale for combining signal transduction inhibitors and hormonal agents [98].

In conclusion, as the therapeutic window becomes wider with the advent of new hormonal drugs and targeted therapies, new options will need to be studied in elderly patients. In general, endocrine therapy should be continued for as long as possible in older patients, until their metastases are convincingly refractory to such treatment, delaying the use of chemotherapy.

Chemotherapy. Which chemotherapy regimen or single drug is the best approach in the metastatic setting is not yet known for the elderly population. While polychemotherapy regimens are usually tested for younger patients, the fear of severe, and often unexpected, toxicities limits the treatment of the older ones. Combination versus sequential single-agent therapy in metastatic breast cancer remains an open question. Sequential therapy allows the optimal delivery of single drugs, potentially reducing the risk of toxicities and improving quality of life. This probably is the most important goal for a patient who has, in any case, a limited life-expectancy.

Age is the main risk factor for doxorubicin-related CHF [99], with older patients showing a greater incidence of CHF after a cumulative dose of 400 mg/m². This dose is superior to what is expected with four standard doses of adjuvant treatment, but Li et al. [100] have recently shown that the initial concentrations of doxorubicin following intravenous administration are higher in older people because of a age-related decrease in the distribution clearance. The majority of the literature data on chemotherapy in elderly patients is derived from single-center phase-II trials involving less than 100 patients, not allowing firm conclusions on the real effectiveness of different drugs to be drawn.

Several drugs, such as taxanes in weekly schedules [101,102], gemcitabine [103], mitoxantrone [104], vinorelbine [105], capecitabine [106] idarubicin [107], were recently tested in elderly metastatic patients with different activity and toxicity profiles (Table III).

Table II. First line endocrine therapy in older women with advanced breast cancer comparing fulvestrant and aromatase inhibitors with tamoxifen.

	Fulvestrant F vs T ⁽⁹⁶⁾	Anastrozole A vs T ⁽⁹⁰⁾	Letrozole L vs T ⁽⁹¹⁾	Exemestane E vs T ⁽⁹²⁾
No of patients	313 vs 274	511 vs 510	453 vs 454	190 vs 192
Obj. Resp. %	31.6 vs 33.9	29.0 vs 27.1	32* vs 21	44.2 vs 29.2
Clin. Benefit % (ER/PgR pos.)	54.3 vs 62.0* (57.1 vs 62.7)	57.1 vs 52.0	50* vs 38	71.6 vs 65.2
Med PFS (mos) (ER/PgR pos.)	6.8 vs 8.3 (8.2 vs 8.3)	8.5 vs 7.0 (10.7* vs 6.4)	9.4* vs 6.0	10.9* vs 6.7

*statistically significant.

Liposomal doxorubicin is very interesting in the setting of older patients for the reduced toxic effects [108,109].

New target therapies. The new therapies with monoclonal antibodies, namely trastuzumab (directed against the extracellular domain of HER2 receptor) and bevacizumab (directed against VEGF-Vascular Endothelial Growth Factor), are new exciting options in the medical oncology armamentarium and have proved their activity in advanced breast cancer usually in combination with cytotoxic agents like taxanes [110,111]. Only very few and selected elderly patients were treated so far. Therefore, there is an urgent need of data on this peculiar topic. Furthermore, the recently reported laboratory studies on potential mechanisms of resistance to endocrine therapies involving cross-talk between growth factor signalling pathways and ER [112] open the hypothesis of combining ER-targeted therapies with growth factors inhibitors and may represent an extraordinary promising approach for future trials also in elderly patients.

Symptom management. Symptom management in older patients affected by breast cancer may differ from that of younger patients. For example, pain, frequently associated with bone metastases, is often inadequately treated due to the fear of major adverse effects from opioids use (drowsiness, hallucinations, constipation). Morphine, on the contrary, is a good choice of agent in elderly patients. Moreover, elderly may suffer from many causes of pain, because they frequently have multiple pathologies, and this implies preexistent use of FANS. The use of analgesics in the elderly population may be difficult also due to pharmacologic interactions (polipharmacy).

Bisphosphonates are recommended for all patients with lytic bone metastases and should be part of the treatment irrespective of age. Although no substitute for adequate analgesia, along with a wide range of

other interventions, may play a helpful part in pain management in the elderly breast cancer patients.

Antiemetic therapy remains also extremely important in elderly patients because the consequences of severe emesis are likely to be more serious than in younger patients. Protracted nausea and vomiting can result in life-threatening dehydration and electrolyte imbalance, which is particularly important in patients who may already have cardiovascular problems [113]. In addition, older patients tend to have a decreased thirst reflex and so are more at risk of dehydration than younger patients.

Neutropenia and anemia may limit the use of chemotherapy in older breast cancer patients. The guidelines of the ASCO recommend primary prophylaxis with hematopoietic growth factors when the risk of febrile neutropenia exceeds 40%. However, the guidelines also recommend the first-cycle use of growth factors in "special" patient populations. It has been advocated that all patients aged 70 years or older should be included in this definition [114].

At its 2001 meeting, the International Society for Geriatric Oncology (SIOG) recommended that G-CSF and other supportive therapies, such as erythropoietic agents, should be considered an integral and essential part of therapy for the elderly patients with cancer being treated with either curative or palliative chemotherapy [115].

Ultimately, the incidence of mucositis is higher in the elderly, particularly those who are treated with intravenous fluoropyrimidines [81]. Older patients should be monitored closely and be taught to recognize the symptoms of diarrhea, cystitis, gastritis, and stomatitis. Mucositis should be treated aggressively with prompt fluid resuscitation when the patients become unable to eat or diarrhea develops; otherwise, dehydration may become life-threatening.

Conclusions

There has been a significant increase in the number of studies conducted in older patients with cancer.

Table III. Activity of single drugs in older patients with metastatic breast cancer.

Study	Drug	No of Pts	Median Age	Pretreated (%)	CR+PR (%)	Neutropenia Grade 3-4 (%)
Hainsworth [101]	Docetaxel Weekly	41	74	25	36	2 (4.8)
Del Mastro [102]	Weekly Taxol	46	70	0	54	4 (8.8)
Feher [103]	Gemcitabine	198	69	0	16	47 (25.3)
	Epirubicin	199	68	0.5	40	34 (17.9)
Repetto [104]	Mitoxanttrone	27	77	0	26	2 (8)
Vogel [105]	Vinorelbine	56	72	0	38	14 (25)
Bajetta [106]	Capecitabine	73	73	10	27	1 (2%)
Crivellari [107]	Idarubicin	47	75	0	22	4 (12)

Although available age-specific clinical trials data demonstrate that treatment efficacy is not modified by age, this evidence is limited by the lack of inclusion of substantial numbers of older women, particularly those of advanced age and those with comorbidities. Investigators are exploring practical means of improving the accrual of older patients in clinical trials. Possible interventions are physicians' education and the employment of a Complete Geriatric Assessment prior to start any therapeutical intervention, in order to enable a patient-tailored treatment. Given its negative effect on the quality of life, in the last few years the role of adjuvant radiotherapy has been questioned in elderly patients after BCS. As pharmacological treatment is concerned, new "elderly-friendly" drugs, that can help clinicians to reduce toxicity, are now available. Adjuvant chemotherapy benefit in older patients applies mainly to ER-negative patients [77], while in ER-positive patients a major role is played by endocrine treatment [78]. Surgical treatment in older patients has evolved from avoidance to mastectomy to BCS, similarly to younger patients. Surgeons treating elderly cancer patients need to realize that functional status is more important than age. If this happens, the increased number of surgical options in elderly cancer patients should lead to an increase in overall cancer survival and contribute to an improvement in their QOL.

Older patients are better treated today than they were a few years ago, and, hopefully, in the future older patients will be able to receive the best of care, similarly to their younger counterpart.

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