

# Chemotherapy of Breast Cancer in the Elderly

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**Abstract:** Breast cancer arises in about 48% of patients older than 65 years and more than 30% occurs in those over 70 years being the leading cause of cancer-related death in women older than 65. Elderly patients tolerate chemotherapy poorly compared to their younger counterpart because of progressive reduction of organ function and comorbidities related to age. For this reason, the elderly have been excluded from or underrepresented in most cancer studies and, in clinical practice, they often receive inadequate and untested treatments. For adjuvant chemotherapy, a low percentage of patients over 70 years of age were included in few trials and always in a proportion much lower than the prevalence of cancer in that age group. Adjuvant chemotherapy, preferably including an anthracycline especially in patients with HER-2/neu-positive tumours, seems to be beneficial in older women who have substantial risk of dying of breast cancer. To date even if there is no specifically randomised study, single-agent chemotherapy probably might be considered a reasonable treatment for advanced breast cancer in the elderly. One of the actual main field of clinical research in the treatment of breast cancer is the role of targeted therapies. Chronologic age is a risk factor for toxicities such as myelosuppression and mucositis, and older patients may require more supportive care. In order to plan medical treatment in breast cancer elderly patients is mandatory to practice a comprehensive geriatric assessment that includes evaluation of comorbidities, functional dependence, socio-economic, emotional and cognitive conditions, an estimate of life expectancy and recognition of frailty. The authors review the literature regarding age-specific chemotherapeutic issues in the management of breast cancer elderly patients.

**KEYWORDS:** Breast cancer, elderly patients, chemotherapy.

## INTRODUCTION

Breast cancer in the elderly has attracted considerable interest in the recent years also because it is becoming a great social problem. Increasing age is a major risk factor for developing breast cancer, peaking at about age 75 and then declining slightly. The prevalence and incidence of breast cancer in older women may increase by 30% over the next decade if the expansion of the older population continues at the present rate [1]. Data from the Surveillance, Epidemiology and End Results (SEER) Program show that 37% of the patients with breast cancer diagnosed in 1973 were 65 years or older compared with 46.7% in 1995 [2]. Breast cancer arises in about 48% of patients older than 65 years and more than 30% occurs in those over 70 years. Breast cancer mortality is declining by 8% in the US and 3% in Europe, although the decline is smaller in elderly patients than in younger ones, and thus leaving open questions on diagnosis and treatment approaches [3].

The efficacy of adjuvant chemotherapy in older women with breast cancer is a complex issue. The ability of adjuvant chemotherapy to reduce disease-related mortality declines with increasing age and infirmity [4]. An important consideration related to the trials of postmenopausal women concerns the low percentage of patients over 70 years of age. Patients in this age group were included in only a few adjuvant trials and always in a proportion much lower than

the prevalence of cancer in that age group. Adjuvant chemotherapy seems to be beneficial in older women who have substantial risk of dying of breast cancer [5].

Chemotherapy is indicated in elderly patients with advanced breast cancer (ABC) resistant to hormonal treatment or with visceral metastases. Anyway, physicians are less likely to offer chemotherapy to their older breast cancer patients presumably because of perceived poorer tolerance, greater risks associated with myelosuppression, and reduced efficacy compared with younger patients. When given the option, older women are less likely to accept chemotherapy presumably because of concerns regarding subjective side effects such as alopecia, nausea and vomiting [6]. Nonetheless, due to physiologic reduction of functional organ reserve and presence of comorbid conditions, elderly patients are often unsuitable for a standard polichemotherapy as used in their younger counterpart. Consequently, they are usually excluded from clinical trials as well. Elderly patients with breast cancer frequently suffer from tumour-related symptoms and need some kind of palliative treatments. In clinical practice, they often receive inadequate and untested treatments [7, 8].

This article reviews the literature regarding age-specific chemotherapeutic issues in the management of breast cancer elderly patients.

## AGE CUT-OFF

Within epidemiological literature the age of 65 is usually considered as a cut-point to select elderly population. On the contrary, in clinical trials, the age of 70 is frequently used as lower limit for patients selection. A cut-off age of 75 years is

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less common. Indirect comparison of trials including or not patients aged 65 to 70 may be biased. A further bias may be due to the distribution of the so called "very old" patients, aged 80 or more [2]. Furthermore we must consider that is very difficult to establish a maximum age for chemotherapy in the elderly. In clinical practice biological instead of chronological age should be considered. Unfortunately, to date, laboratory tests and geriatric evaluation are inadequate to define ageing; therefore, at the present, chronological age should be used as frame of reference for clinical trials. A cut-off of 70 years seems to be the most appropriate. In fact, 70 years of age may be considered as the lower boundary of senescence, because the incidence of age-related changes starts to increase after the age of 70 years [9].

## COMORBIDITIES AND FRAILITY

The correct assessment of a cancer patient is a key step in the treatment process. The data indicate that the clinical outcome in each type of cancer is predicted not by age itself but by the degree of comorbidity and functional decline that may be present. In fact, elderly patients tolerate chemotherapy poorly because of comorbidities and organ failure. Elderly patients who are otherwise healthy can obtain the same benefits from chemotherapy as younger patients. Furthermore, older patients are as able as younger patients to tolerate chemotherapy, but their management may require more attention to supportive care. Preliminary observation on cancer patients also confirm the coexistence of other disease in elderly cancer patients [2]. Comorbidities are serious medical conditions that are not directly related to the cancer itself but involve mainly metabolism or cardiovascular, respiratory, renal and hepatic system. These conditions are usually chronic morbidity and can also adversely affect patient functional status.

Another important issue is the definition of frail elderly persons. The frailty can be defined as a condition in which

most functional reserve is exhausted and that makes persons susceptible to even minor stresses. Frail patients are those who depend on others for the activities of daily living prevalently because of physical and cognitive dysfunction. With the expansion of the older population, the number of frail elderly and frail elderly with cancer is expected to rise. According to a conservative estimate, approximately 400.000 frail elderly in United States are affected by some form of cancer at any given time. Moreover, frailty is not equivalent to near death in fact, the average life expectancy of a frail person is in excess of 2 years [10, 11]. Generally in these group of patients chemotherapy should be avoided. Reliable information regarding patient comorbid health problems is mandatory in order to plan an appropriate treatment. However, to date, a standard, fully satisfactory way to assess co-morbidity has not been defined [12]. A better understanding of the effects of chemotherapeutic agents on older patients and increased knowledge of pharmacokinetic data will help to determine their appropriate use in the elderly [13].

In order to plan medical treatment in breast cancer elderly patients, and to further individualise treatment choice, is mandatory to practice not only the patient's basic medical history and the standard cancer staging, but also a comprehensive geriatric assessment (CGA). The CGA includes assessment of comorbidity, socio-economic conditions, functional dependence, emotional and cognitive conditions, an estimate of life expectancy and recognition of frailty. All these various facets of the patient's health and environment may interfere with therapy. The choice of the drug should be based on the evaluation of both toxicity profile of each drug and on the patient CGA. The basic component of CGA are presented in Table 1 [5].

The role of CGA in clinical practice was recently reinforced by the results of a pilot study in which 15 early breast cancer patients were enrolled. The patients, aged 70

**Table 1. Elements of a Comprehensive Geriatric Assessment (CGA)**

Parameter assessed	Elements of the assessment
Function	Performance status Activities of daily living (ADL) Instrumental activities of daily living (IADL)
Comorbidity	Number of comorbid conditions Severity of comorbid conditions (comorbidity index)
Socio-economic conditions	Living conditions Presence and adequacy of a caregiver
Cognition	Folstein mini-mental state evaluation Other tests
Emotional conditions	Geriatric depression scale (GDS)
Pharmacy	Number of medications Appropriateness of medications Risk of drug interactions
Nutrition	Mini-nutritional assessment (MNA)
Geriatric syndromes	Dementia Delirium Depression Falls Neglect and abuse Spontaneous bone fractures

and older, received a multidisciplinary CGA every 3 months and structured follow-up lasting 6 months. All patients were analysed after their initial surgery, and prior to initiation of their adjuvant radiation therapy and systemic treatment. This pilot study showed that in several patients this intervention had a direct or indirect impact on their cancer care. This interesting results needed to be further explored in a randomized trial [14].

There is clear evidence that the CGA improves the function and quality of life and promotes the independence of older patients, but its effect on survival is not clear [15, 16]. Anyway, a CGA should detect important conditions that are associated with short survival. Simple ways of predicting mortality have been proposed by Walter *et al.* For mortality in the short term (within 1 year), a scoring system that includes function, cardiovascular comorbidity and cancer is very accurate [17]. For mortality in the longer term, the geriatric assessment can be integrated with life-table estimates [18].

## AGING AND BIOLOGY OF BREAST CANCER

Aging has an impact on cancer biology and behaviour. Recently, some studies have evaluated if breast cancers occurring in the elderly were associated with biologic characteristics and prognosis different from those occurring in young. It is so, this difference may be the rationale for a management of the elderly patients different from that of the young ones. Two studies evaluated several biological characteristics or only the hormonal receptor profile on primary tumours from 35,154 patients 55 years or older from San Antonio breast cancer database or from 19,541 non-Hispanic white women with node-negative breast cancer from SEER database. These data confirm the association of advanced age with favourable biological features and demonstrates that, in elderly women with early (small size and/or node negative) breast cancers, survival is superimposable to that of the general population, regardless of the disease status [19, 20]. Another trial revised the biological characterisation on 14,007 primary breast cancers providing evidence in favour of a relation between advanced age and favourable features (positivity for oestrogen/progesterone receptors, low proliferative rate, absence of p53 accumulation, bcl-2 overexpression, diploid DNA content). It showed also a similar pattern of association between patho-biological variables regardless of patients age and a relation between biological variables and disease outcome in the elderly, comparable to that reported for younger patients [21]. The presence of biological features characterising an indolent disease and the favourable outcome of elderly patients regardless of disease status should be taken into consideration when making clinical decision. A higher proportion of the tumours in elderly women are of a more indolent type, such as papillary carcinoma. The incidence of invasive lobular carcinoma is increasing among post-menopausal women. In fact, this histologic type was uncommon in post-menopausal women during prior decades when hormone replacement therapy use was infrequent. The increasing administration of hormone replacement therapy in post-menopausal women was related to increasing incidence up to 4-fold of invasive lobular carcinoma from 1974 to 1995 whereas the incidence of invasive ductal carcinoma increased

steadily from 1977-1987 and have plateaued since 1987 [22]. Moreover, patients with invasive lobular carcinoma, aged 50 to 79, had a risk of mortality 11% lower than women with invasive ductal carcinoma. Also the risk of mortality was between 8% and 34% lower in women with mucinous carcinoma, comedocarcinoma, or medullary, tubular, and papillary carcinomas compared with women with invasive ductal carcinoma [23]. Another epidemiologic trial evaluated the lobular carcinoma *in situ* incidence rates that have steadily increased from 1978 to 1998 only among post-menopausal women [24].

## TREATMENT RELATED TOXICITY

Age-related physiologic changes and the higher prevalence of comorbidities in older patients increase the toxic effects of chemotherapy such as neutropenia, anaemia, mucositis, cardiomyopathy and neuropathy [11, 13]. Polypharmacy and high drug use are common in elderly. Drugs used to treat comorbidities may interact with chemotherapeutic regimens exacerbating their toxicity [25]. In fact, many anticancer drugs are metabolized by cytochrome P450 enzymes, which can be induced or inhibited by many commonly prescribed medications, such as opioids, antidepressants and antipsychotics [26]. Therefore, drug interactions can be a particular concern in polypharmacy.

Reduced haematopoietic stem-cell mass and reduced ability to mobilize these cells from the marrow in elderly, may slow their recovery after cytotoxic chemotherapy [27]. The manifestations of chemotherapy-induced haematological toxicity include neutropenia, which increase the risk of potentially fatal infections; anaemia, which causes fatigue; and thrombocytopenia, which causes increased bleeding (especially in the presence of age-related vessel fragility).

Life-threatening complications of neutropenia, such as fever and infection, are more frequent in older than in younger patients resulting in more hospitalizations for febrile neutropenia, longer hospital stays and higher mortality. Neutropenia can be managed with granulocyte-colony stimulating factor (G-CSF). National Comprehensive Cancer Network (NCCN) guidelines for the management of elderly patients recommend the routine use of growth factors in patients aged 70 years or older who are treated with moderately aggressive chemotherapy regimens [28]. The 2000 guidelines of the American Society of Clinical Oncology (ASCO) recommend primary prophylaxis with G-CSF when the risk of febrile neutropenia exceeds 40% [29]. The guidelines also recommend the first-cycle use of G-CSF in "special" patient populations such as patients aged 70 years or older.

The influence of haemoglobin levels on drug toxicity is of particular interest. In fact, several of the common chemotherapeutic agents bind to red blood cells. For those drugs that are highly bound to red blood cells, such as taxanes and anthracyclines, anaemia is associated with a greater concentration of free drug in the circulation resulting in an independent risk factor for myelosuppression. In order to avoid unpredictable drug toxicity and the consequence of anaemia, such as fatigue, is advocated to correct anaemia before and after chemotherapy [30]. ASCO and the American Society of Hematology (ASH) developed an evidence-based

clinical practice guideline for the use of epoetin in patients with cancer. The guideline panel found good evidence to recommend use of epoetin as a treatment option for patients with chemotherapy-associated anaemia with a haemoglobin concentration  $\leq 10$  g/dL. For patients with haemoglobin

concentration below 12 g/dL but who have never fallen below 10 g/dL, the decision to use epoetin immediately or to wait until haemoglobin level fall closer to 10 g/dL should be determined by clinical circumstances [31].

**Table 2. Randomised Clinical Trials of Adjuvant Chemotherapy Including Patients Aged  $\geq 65$  Years**

Author	No.pts	Node-status	Treatment	5-year DFS (%)	5-year OS (%)
Ingle, 1988	75	Positive	CTX + 5-FU + PDN	61	NR
	71		Vs	59	NR
	88		CTX + 5-FU + PDN + TAM	43	NR
			Vs		
			Control		
Taylor, 1989	962	Positive	CTX + 5-FU + Methotrexate + PDN + TAM x 12	-	-
			Vs	-	-
			CTX + 5-FU + Methotrexate + PDN + TAM x 4		
Fisher, 1990	1124	Positive	TAM	67 (3-yr)	85 (3-yr)
			Vs	84 (3-yr)	93 (3-yr)
			ADM + CTX + TAM	83 (3-yr)	92 (3-yr)
			Vs		
			Melphalan + ADM + 5-FU + TAM		
Schumacher, 1994	328	Positive	CTX + Methotrexate + 5-FU x 3 $\pm$ TAM	-	-
			Vs	-	-
	235		CTX + Methotrexate + 5-FU x 6 $\pm$ TAM		
Rivkin, 1994	966	Positive	CTX + Methotrexate + 5-FU + VCR + PDN + TAM	-	75
			Vs	-	78
			CTX + Methotrexate + 5-FU + VCR + PDN	-	77
			Vs		
			TAM		
Crivellari, 2000*	93	Positive	TAM	61	80
			Vs	63	77
	79		CTX + Methotrexate + 5-FU x 3 + TAM		
Wils, 1999	604	Positive	TAM	62.1	77
			Vs	73.7	80.6
			EDX + TAM		
FASG, 2001	289	Positive	5-FU + EDX (50 mg/m <sup>2</sup> ) + CTX	54.8	65.3
			vs	66.3	77.4
	276		5-FU + EDX (100 mg/m <sup>2</sup> ) + CTX		
Albain, 1997	361	Positive	TAM	72 (4-yr)	85 (4-yr)
			Vs	79 (4-yr)	86 (4-yr)
			CTX + ADM + 5-FU TAM	79 (4-yr)	86 (4-yr)
			Vs		
	563		CTX + ADM + 5-FU + TAM		
	546				
Fargeot, 2003**	164	Positive	TAM	73.5	-
			Vs	77.9	-
	174		EDX + TAM		
Mansour, 1989	406	Negative	Control	69 (3-yr)	-
			Vs	84 (3-yr)	-
			CTX + Methotrexate + 5-FU + PDN		
Fisher, 1997	771	Negative	TAM	85	94
			Vs	90	97
			Methotrexate + 5-FU + TAM	89	96
			Vs		
	767		CTX + Methotrexate + 5-FU + TAM		
	768				
IBCSG, 2002	1217	Negative & ER-positive	TAM	85	93
			Vs	84	95
			CTX + Methotrexate + 5-FU TAM		
IBCSG, 2002	382	Negative & ER-negative	TAM	69	81
			Vs	84	89
			CTX + Methotrexate + 5-FU TAM		

DFS = disease-free survival; OS = overall survival; NR = not reached; 5-FU = 5-fluorouracil; CTX = cyclophosphamide, PDN = prednisone; TAM = tamoxifen; ADM = adriamycin; VCR = vincristine; EDX = epirubicin; FASG = French Adjuvant Study Group; IBCSG = International Breast Cancer Study Group; ER = oestrogen receptor; \*data referred to patients  $\geq 65$  years; \*\*randomised trial addressed to patients aged  $> 65$  years.

Increased destruction of and lower numbers of rapidly renewing mucosal stem cells increase susceptibility to mucositis [25, 32]. The incidence of mucositis such as cystitis, gastritis and stomatitis, which often lead to diarrhoea, is higher in the elderly [33]. Mucositis should be treated promptly, with fluid resuscitation when patient becomes unable to eat or diarrhoea develops; otherwise, dehydration may become life-threatening. There is no approved treatment for mucositis, but recombinant keratinocyte growth factors have shown promise in randomised controlled studies, reducing the incidence and severity of mucositis by 40% [34]. AES-14, a new drug-delivery system of l-glutamine to oral mucosa that is at risk for ulceration, is a new method for relieving mucositis [35].

The greater incidence and severity of toxicity in the elderly mean that they require more supportive care. The prediction of which older patients are at greatest risk of toxicity associated with chemotherapy would be clinically valuable. Unfortunately, the pharmacokinetic modelling that is useful for predicting the toxicity of some drugs, may be impractical in clinical practice, may be difficult to determine with multidrug regimens, and may be inadequate with non-pharmacokinetic mechanisms of toxicity such as reduced stem-cell reserves [36].

## LITERATURE REVIEW

All published papers specifically addressing chemotherapy of elderly breast cancer patients until July 15, 2004 were searched using MEDLINE (PubMed, National Library of Medicine, Bethesda, MD, USA; used keywords: breast cancer, elderly patients, chemotherapy). Therefore, all published papers in medical journals were reviewed and all abstracts presented at the last main international meetings were considered.

### Early Breast Cancer

Adjuvant treatment for elderly women affected by breast cancer is one of the most questionable issues in clinical oncology. The use of tamoxifen (TAM) in patients with hormone receptor-positive tumours is a relatively simple therapeutic option considering the favourable toxicity profile. According to the data of Oxford overview, the benefit of adjuvant TAM is age independent. Therefore, TAM for a 5-year period represents the standard treatment proposed to endocrine responsive patients [37]. There is consensus on the use of adjuvant chemotherapy in patients with breast cancer younger than 70 years, but not on its use in older women. The addition role of adjuvant chemotherapy in hormone receptor-positive or -negative breast cancer elderly patients is an extremely debated issue. The administration of adjuvant chemotherapy is more complicated and a variety of aspects need to be considered such as the estimated life expectancy, the presence and degree of comorbidities, the geriatric assessment and estimated benefit from treatment. The Early Breast Cancer Trialists' Collaborative Group explored the activity of adjuvant chemotherapy in a meta-analysis. The benefits of adjuvant chemotherapy in terms of survival and freedom from progression declined with the patient age, and no benefit were seen in patients aged 70 or older. However, the oldest group of patients represented less

than 4% of the total post-menopausal population, which is too small to draw firm conclusions [38]. In the 7<sup>th</sup> International Consensus Conference of St. Gallen the panel recommended to consider the elderly patients within post-menopausal group because survival rate is prevalently related to tumour characteristics and comorbidities and not to patient age [39].

Many prospective randomised clinical trials employed adjuvant chemotherapy in post-menopausal women, but an important consideration concerns the underrepresentation, in these studies, of women over 70 years of age. Women in this age group were included in only few trials and always in a proportion much lower than the prevalence of cancer in that age group [5]. Table 2 summarises the results of randomised trials in which also patients aged  $\geq 65$  years, node-negative and -positive, were enrolled [33, 40-51].

In particular, Crivellari *et al.* reported data specifically related to patients aged 65 years and old randomised to receive TAM (93 patients) alone for 5 years (20 mg, p.o.) or 3 cycles of cyclophosphamide (100 mg/m<sup>2</sup>, p.o., from day 1 to 14) plus methotrexate (40 mg/m<sup>2</sup>, i.v., day 1 and 8) plus 5-fluorouracil (600 mg/m<sup>2</sup>, i.v., day 1 and 8) (CMF regimen; 79 patients), recycled every 4 weeks plus TAM. In the CMF arm, more women in the older age experienced grade 3 toxicity of any type as compared to younger ones (17% vs 7%, respectively). The distribution of grade for both hematologic toxicity ( $p = .0002$ ) and mucositis ( $p = .004$ ) were significantly higher for patients 65 years or older. For older patients the 5-year disease-free survival (DFS) rates were 63% for CMF plus TAM and 61% for TAM alone ( $p = .99$ ). The 5-year overall survival (OS) was 80% for TAM arm and 77% for chemo-endocrinotherapy [33]. Given the relatively few patients  $\geq 65$  years old who were enrolled in this trial, it is uncertain whether the effectiveness of CMF in the elderly cohort is actually as modest as these data that seem to confirm the results of the overview of polychemotherapy for early breast cancer, where a gradual decrease of the benefits is notable with increasing age [38]. The International Breast Cancer Study Group (IBCSG), randomised 1,699 postmenopausal women with lymph node-negative breast cancer to receive either 5 years of TAM alone or 3 cycles of CMF followed by 5 years of TAM. The patients were stratified by oestrogen receptor (ER) status. This design created two studies within the same trial: one study examining the role of CMF followed by TAM versus TAM alone in 1,217 postmenopausal patients with ER-positive breast cancer and a second study comparing the same regimens in 382 women with ER-negative breast cancer. The results indicate no benefit from the addition of chemotherapy to TAM in the larger ER-positive group but show a statistically significant and meaningful survival benefit in the smaller ER-negative subset [51]. These data reinforce the caution regarding the use of chemotherapy in patients with ER-positive disease who will receive 5-years of adjuvant TAM therapy [52]. A recent meta-analysis involving 2,368 post-menopausal women showed that CMF regimen improved by 5.5% the DFS with no effect on OS [53]. But, analysing the data from these trials emerges that women with hormone-receptor poor tumours may benefit from the less toxic CMF-like chemotherapy, whereas women with receptor-rich tumours appear to benefit from adjuvant chemotherapy only when an anthracycline is included. A

possible explanation for this data is that in patients with overexpression of HER-2/neu is probably preferable an adjuvant anthracycline-based chemotherapy [5].

Recently, a phase III trial randomised 338 patients aged 65 years or older after surgery and with node-positive to receive TAM alone (30 mg/day, p.o.) for 3 years or epirubicin (EDX; 30 mg/m<sup>2</sup>, i.v., day 1, 8 and 15), every 4 weeks plus TAM for 3 years. After a median follow-up of 64 months, there were 26.5% of relapse with TAM versus 22.1% with EDX plus TAM. The median time to relapse was of 19 and 33 months, respectively (p = .07). The chemotherapy was well tolerated with no grade 3-4 hematologic toxicity, and 5 cases of left ventricular ejection fraction decreases occurred [48].

Due to the lack of data from clinical trials in women over the age of 70, the approach is still experimental. Muss *et al.* analysed data from 6,489 patients entered on the Cancer And Leukemia Group B (CALGB) adjuvant trials 7581, 8082, 8541, 9344. The patients aged  $\geq 65$  years were only 542 (8.3%) and when compared to younger women with node-

positive, they had: higher stage breast cancer, similar dose-related benefits in reducing breast cancer-related relapse and mortality, significantly (p < .05) higher overall mortality due to an increase in non-breast cancer related deaths [54]. A recent trial reviewed 407 breast cancer patients aged  $\geq 80$  years of which 48 (12%) had no treatment, 132 (32%) received TAM alone, 28 (7%) had breast-conserving surgery, 133 (33%) had mastectomy, 57 (14%) had breast-conserving surgery plus adjuvant therapy and 9 (2%) received miscellaneous treatments. Five-year specific breast cancer survival was 46%, 51%, 82% and 90% for women with no treatment, TAM alone, mastectomy and breast-conserving surgery plus adjuvant therapy, respectively. About half of women were undertreated, with strongly decreased specific survival as a consequence. Treatments need to be adapted to the patient's health status, but also should offer the best chance of cure [55]. Clinical trials evaluating the role of adjuvant chemotherapy are currently being developed and hopefully in the near future, more convincing data will become available considering also the advent of new aromatase inhibitors.

**Table 3. Results of Single Agent Chemotherapy in Advanced Breast Cancer Elderly Patients**

Author	No.pts	Age (years)	Drug	RR (%)	MTP (mos)
Chevallier, 1990	31	$\geq 70$	Idarubicin	26	2.7
Provè, 1998	29	> 65	Idarubicin	24	8.5
Toffoli, 2002	20	> 65	Idarubicin	25	-
Chevallier, 1992	30	$\geq 70$	Pirarubicin	25	3
Repetto, 1995	27	$\geq 68$	Mitoxantrone	26	6
Repetto, 2002	29	> 70	Paclitaxel	55	-
Perez, 2002	73	$\geq 65$	Paclitaxel	20	7.1
Zanetta, 2000	4	> 70	Docetaxel	0	-
Constenia, 1999	14	> 65	Docetaxel	71	-
D'hondt, 2000	29	60*	Docetaxel	21	-
Hainsworth, 2001	41	> 65**	Docetaxel	36	7
Massacesi, 2003	28	> 65	Docetaxel	32	11
O'Shaughnessy, 1998	62	$\geq 55$	Capecitabine	25	-
	33		Vs CMF	16	-
Procopio, 2003	62	> 65	Capecitabine	36	2.5
Minea, 2004	63	> 65	Capecitabine	26.9	3.5
Longo, 2004	18	> 65	Capecitabine	28	-
Sorio, 1997	25	> 65	Vinorelbine	30	-
Buonadonna, 1998	38	> 65	Vinorelbine	39.5	7
Vogel, 1999	56	$\geq 60$	Vinorelbine	38	6
Rossi, 2003	24	$\geq 70$	Vinorelbine	37.5	5
Litwiniuk, 2003	44	$\geq 65$	Vinorelbine	36	5
Perez Manga, 2004	48	73*	Vinorelbine***	50	11.6

RR = response rate; MTP = median time to progression; \*median age; \*\*younger patients with poor performance status included; \*\*\*plus letrozole.

### Locally Advanced Breast Cancer

The goal of neoadjuvant chemotherapy is to reduce tumour size in order to increase the percentage of patients undergoing to a breast-conserving treatment and to improve survival. The available randomised trials suggest that neoadjuvant chemotherapy reduce the use of mastectomy, but not improve survival [56-59]. Two randomised trials explored primary treatment with TAM alone in women aged 70 or older both reporting that the breast cancer-related mortality increased for patients who had not received initial surgical treatment [60, 61]. Recently, 50 patients aged 60 years or older, ER-positive with a locally advanced breast cancer received as neoadjuvant treatment vinorelbine (VNR) (30 mg/m<sup>2</sup>, i.v., day 1 and 8, every 3 weeks) plus TAM (20 mg/day, p.o.). Among 44 evaluable patients a RR of 84% was reported with surgery performed in 87% of cases with 9% of pathological complete response. The treatment was well tolerated with grade 3-4 neutropenia in 17% of patients, constipation in 4%, and one toxic death due to neutropenic fever [62].

The definitive role of neoadjuvant chemotherapy in operable breast cancer remains an experimental approach still under investigation in general patient population and should not be considered in clinical practice, outside of a clinical trial, in patients suitable for breast-conserving treatment. To date this therapeutical approach is reasonable in case of large tumour necessitating mastectomy with patient desiring breast-conserving treatment.

### Advanced Breast Cancer

Our literature search found 40 studies. Twenty-six of them have been published as abstract at main international meetings and 14 have been published as extended papers. One trial only was a phase III randomised study. The Table (3) and (4) summarised the results of single-agent and combination chemotherapy, respectively.

#### Single-Agent Chemotherapy

Twenty-three trials of single-agent chemotherapy were reported. Three trials used single-agent oral idarubicin (IDA). Chevalier *et al.* on 30 elderly patients (> 70 years) with ABC using IDA (15 mg/m<sup>2</sup>, p.o., d 1, 2, 3, every 3 weeks) reported a RR of 26% with a median duration of response (MDR) of 2.7 months [63]. Provè *et al.* treated 29 elderly patients failing hormonal therapy with IDA (20 mg/m<sup>2</sup>/week x 4, p.o.). The Authors reported a RR of 24% with MDR of 8.5 months and mild toxicity consisting, mainly of myelosuppression [64]. Toffoli *et al.* used IDA on 14 elderly patients, at the dose of 5 mg/day and 10 mg/day every other day, p.o., for 21 days, recycled every 4 weeks. Due to excessive toxicity (grade 3-4 neutropenia occurred in 64% of patients), 5 mg/day for 21 day, p.o., every 4 weeks was given in further 12 patients. RR of 25% was reported in 20 evaluable patients with MDR of 6 months and the Authors indicated that 5 mg/day is a safe effective dosage for older patients [65].

Another trial by Chevalier *et al.* using single-agent pirarubicin (30 mg/m<sup>2</sup>, i.v., d 1, every 3 weeks) on 31 elderly patients reported 25% RR with a median time to progression (TTP) of 3 months [66].

Repetto *et al.* using mitoxantrone (MITO) (10-14 mg/m<sup>2</sup>, i.v., d 1 every 3 weeks), reported 26% PR among 27 patients aged  $\geq$  68 years; MDR and OS were 6 and 8 months, respectively [67].

In a dose-finding phase I study, paclitaxel (TAX) was administered in one-hour infusion at a starting dose of 60 mg/m<sup>2</sup> day 1, 8 and 15 every 4 weeks. The dose was escalated to 10 mg/m<sup>2</sup>. A total of 12 patients were treated and the dose of 80 mg/m<sup>2</sup> was considered safe and feasible in elderly patients [68]. The same author in the followed phase II trial, administered TAX at the dose of 80 mg/m<sup>2</sup>, i.v. day 1, 8 and 15 every 4 weeks in 29 elderly patients with ABC. The reported results were 3 complete and 13 partial responses for an overall RR of 55% with mild toxicity [69]. Perez *et al.* evaluated, retrospectively, the activity of TAX 80 mg/m<sup>2</sup>, i.v., weekly for 4 weeks per 4-week cycle, in 73 ABC patients (71% pretreated) aged more than 65 years enrolled in a large phase II trials. RR 20%, 12.7 months of median survival and mild toxicity (grade 3-4 neutropenia in 15% and grade 3 neuropathy in 13% of patients) were observed [70]. Smorenburg *et al.* studied the pharmacokinetics of TAX 80 mg/m<sup>2</sup>, i.v., in 8 elderly patients ( $\geq$  70 years) as compared to 15 younger treated with TAX 100 mg/m<sup>2</sup>, i.v. The data indicated an approximately 50% change in total body clearance of unbound TAX and a concomitant significant increase in systemic exposure with age. These observations require further evaluations [71].

Single-agent docetaxel (TXT) has been tested in 2 different schedules: every 3 weeks and weekly. In a phase I trial 4 patients older than 70 years were treated with escalating dose of TXT (75, 85, 90, 95 and 100 mg/m<sup>2</sup>) given every 3 weeks. The Authors stopped the study after the first 4 patients enrolled at the first dose-level due to toxicity and reporting no clinical response. They concluded that TXT at 75 mg/m<sup>2</sup> and over, every 21 days, is too toxic in the elderly [72]. On the contrary, Constenla *et al.* treated 14 elderly patients (> 65 years, six of which frail) with TXT at 75 mg/m<sup>2</sup> and 100 mg/m<sup>2</sup>, every 3 weeks, with lenograstim support. They reported a RR of 71% with acceptable hematological toxicity [73]. Two trials investigated weekly TXT. D'hondt *et al.* administered weekly TXT at the dose of 36 mg/m<sup>2</sup> in 29 elderly or younger unfit patients, mostly heavily pretreated. The median age was 60 years and the RR was 21% with a good tolerability [74]. In another phase II study, TXT (36 mg/m<sup>2</sup>) was administered weekly for 6 weeks in 41 elderly or poor performance status patients with ABC. The reported RR was 36% with a 72% of disease control, a median TTP of 7 months, a median OS of 13 months and with 1- and 2-year actuarial survival rate of 61% and 29%, respectively. Most common toxicity was grade 3-4 fatigue occurred in 20% of patients [75]. Recently, TXT was administered to 28 pretreated elderly patients (> 65 years) in 3 different schedules: 25-30 mg/m<sup>2</sup>, i.v., every 7 days; 50 mg/m<sup>2</sup>, i.v., every 14 days; 75-100 mg/m<sup>2</sup>, i.v., every 21-28 days. The RR was 32%, TTP 11 and OS 20 months with mild toxicity. No significant differences between the 3 schedules were reported [76]. The safety of TXT in older patients was recently examined. The Authors analysed, retrospectively, the data about 81 women aged 65 or more among 544 patients enrolled in 3 trials in which the TXT was administered at the dose of 100 mg/m<sup>2</sup>, i.v., day 1 every 3

weeks. The safety profile of TXT for elderly women was similar to that of younger patients except for an increased incidence, in elderly women, of all grades of anorexia (22%, 9%;  $p = 0.0012$ ) and asthenia (78%, 59%;  $p = 0.0012$ ) and grade 3-4 diarrhoea (15%, 6%;  $p = 0.0117$ ) [77].

Four studies with capecitabine were reported. O'Shaughnessy *et al.* randomised patients in a phase II trial to capecitabine (2510 mg/m<sup>2</sup>/b.i.d., p.o., days 1 to 14, every 3 weeks) or CMF. The study accrued 95 women aged  $\geq 55$  years. Objective response was 25% for capecitabine and 16% for CMF with a median TTP of 132 days and 94 days, respectively. The authors concluded that home-based monotherapy with capecitabine shows at least comparable efficacy to CMF [78]. Procopio *et al.* treated 62 women older than 65 years with capecitabine (2500 and than 2000 mg/m<sup>2</sup>/b.i.d., p.o., day 1 to 14, every 3 weeks). They reported RR of 36% with a median TTP of 2.5 months, one patient died due to gastrointestinal toxicity [79]. Minea *et al.* treated 63 ABC elderly patients with capecitabine at the dose of 1250 mg/m<sup>2</sup>, p.o., twice daily from day 1 to 14 every 3 weeks. Main toxicity was grade 3-4 diarrhoea in 6 patients, grade 3 mucositis and asthenia in 2 and 8 patients, respectively and grade 2-3 hand-foot syndrome in 15

patients. The activity was interesting with RR of 26,9% and a MTP of 3.5 months [80]. In another phase II trial, 18 patients were treated with capecitabine at the dose of 1000 mg/m<sup>2</sup>, p.o., twice daily from day 1 to 14 every 3 weeks. The RR was 28% with 7% of patients reporting grade 3 mucositis and hand-foot syndrome [81].

Six studies reported on single-agent VNR in the treatment of elderly patients with ABC [82-87]. Sorio *et al.* treated 20 patients (> 65 years) with VNR at the dose of 30 mg/m<sup>2</sup>, i.v., as first-, second- and third-line therapy, on days 1 and 8 every 3 weeks, reporting 30% OR [84]. Buonadonna *et al.* reported 39.5% RR with MDR of 7 months and a disease control of 60.5%. The schedule of VNR used was 25 mg/m<sup>2</sup>, on days 1 and 8, every 3 weeks. Median age was 70 years and about 40% of patients were treated as second-line therapy [83]. Vogel *et al.* reported a RR of 38% with MDR of 9 months and a disease control of 76%. VNR was administered at the dose of 30 mg/m<sup>2</sup>, weekly for the first 13 weeks and then every 2 weeks. Median dose intensity of VNR was 20.6 mg/m<sup>2</sup>/week [82]. In our experience, we treated 24 elderly ABC patients with VNR 30 mg/m<sup>2</sup>, i.v. day 1 and 8, every 3 weeks. Nine (37.5%) objective responses (2 complete and 7 partial responses) were observed

**Table 4. Results of Combination Chemotherapy in Advanced Breast Cancer Elderly Patients**

Author	Phase	No.pts	Age (years)	Drug	RR (%)	MTP (mos)
Zaniboni, 1998	II	39	72*	Idarubicin + Cyclophosphamide	37.2	-
Kurtz, 2000	I	19	$\geq 65$	Idarubicin + Cyclophosphamide	21	6.6
Masseroni, 2002	II	18	$\geq 70$	Idarubicin + Citofur + Leucovorin	25	-
Cameron, 2002	I	14	66*	Idarubicin + Capecitabine	42.8	-
Rozzi, 2003	II	18	> 70	Epirubicin + 5-Fluorouracil	50	4
Gladieff, 1996	II	25	> 70	Mitoxantrone + Vinorelbine	22	13
Mammoliti, 1996	II	24	> 65	Mitoxantrone + Levo-leucovorin + 5-Fluorouracil	50	9
Pinotti, 2001	II	27	> 65	Mitoxantrone + Levo-leucovorin + 5-Fluorouracil	22.2	-
van Veelen, 1998	II	28	> 70	Mitoxantrone + Methotrexate	39	6.8
Jagiello-Gruszfeld, 2002	II	30	> 70	Mitoxantrone + Methotrexate	50	6
Bajetta, 1998	II	73	> 70	Doxifluridine + Levo-leucovorin	26	7
O'Rourke, 2002	II	39	$\geq 65$	Paclitaxel + Carboplatin	46	-
Hess, 2002	I-II	36	> 65	Capecitabine + Vinorelbine	50	-
Facchini, 2001	II**	18	> 65	Capecitabine	12.5	-
				Capecitabine + Gemcitabine	50	-
				Capecitabine + Vinorelbine	33.3	-
Rozzi, 2002	II	30	$\geq 70$	Vinorelbine + 5-Fluorouracil	50	4.4
Dinota 2003	II	26	$\geq 65$	Vinorelbine + Gemcitabine	53.8	-
Taylor, 1986	III	181	> 65	Tamoxifen	45	10.4
				Vs	38	7.9
				CMF		

RR = response rate; MTP = median time to progression; CMF = cyclophosphamide, methotrexate, 5-fluorouracil; \*median age; \*\*randomised phase II trial.

with MDR and OS of 7 and 11 months, respectively. VNR given on day 1 and 8, recycled every 3 weeks, has a very similar dose-intensity and seems to be better tolerated as compared to weekly administration [85]. Another group treated 44 patients with VNR 20-25 mg/m<sup>2</sup>, i.v., on days 1 and 8 every 3-4 weeks. The RR was 36%, MDR of 5 months and no grade 4 toxicity was recorded [86]. A phase II study evaluated the combination of VNR (30 mg/m<sup>2</sup>, i.v., day 1 and 8 every 3 weeks) and letrozole (2.5 mg daily, p.o.) in 48 elderly ABC patients. The RR was 50% with grade 3-4 neutropenia in 25%, anemia in 6.2% and liver toxicity in 2% of patients. MTD was of 11.6 months [87].

### Combination Regimens

Among trials of combination chemotherapy, 5 included anthracyclines. Zaniboni *et al.* used an oral regimen with IDA plus cyclophosphamide (CTX) in 39 heavily pretreated breast cancer elderly patients. The treatment was well tolerated with a 37.2% RR [88]. Kurtz *et al.* performed a phase I trial using a fixed dose of CTX (200 mg/m<sup>2</sup>/day, p.o., d 1, 2, 3) and an increasing dose of IDA (10 mg/m<sup>2</sup>/day, p.o., d 1, 2, 3), recycled every 3 weeks, both administered orally. Nineteen patients were treated with myelosuppression as dose-limiting toxicity and maximum tolerated dose reached at 12 mg/m<sup>2</sup>/day. Among 14 patients, 4 (21%) achieved a PR with MDR of 6.6 months [89]. Masseroni *et al.* treated 18 elderly patients ( $\geq 70$  years) with IDA (25 mg, p.o., on day 1, 8, 15) plus citofur (400 mg, p.o., from day 1 to 14) plus folinic acid (FA) (30 mg, p.o., from day 1 to 14), every 4 weeks. The RR was 25% with no grade 3-4 toxicity [90]. In a phase I trial the combination of IDA plus capecitabine was tested. IDA was administered at the dose of 10-12.5 mg/m<sup>2</sup>, p.o., day 1, 2 and 3 and capecitabine 1500-2500 mg/m<sup>2</sup>, p.o., from day 1 to 14, every 21 days. A total of 14 patients with a median age of 66 years were treated reporting RR 42.8% with the dose-limiting toxicity related to the capecitabine [91]. Rozzi *et al.* treated 18 elderly patients ( $> 70$  years) with EDX (25 mg/m<sup>2</sup>, i.v., day 1, 8 and 15) plus protracted infusion of 5-fluorouracil (5-FU) 250 mg/m<sup>2</sup>/day from day 1 to 14, every 21 days. The RR was 50%, MDR 4 months with grade 3-4 neutropenia in 24% and anemia in 19% of patients [92].

Gladiëff *et al.* in a phase II study, treated 25 women older than 70 years with the combination of MITO (10 mg/m<sup>2</sup>, i.v., d 1) plus VNR (20 mg/m<sup>2</sup>, i.v., d 1-8), both recycled every 3 weeks. The RR was 22% with a median TTP of 13 months. The dose-limiting toxicity was myelosuppression with no case of febrile neutropenia [93]. Mammoliti *et al.* used a combination of MITO (10 mg/m<sup>2</sup>, i.v., d 1), 5-FU (500 mg/m<sup>2</sup>, i.v., d 15-16) and levo-leucovorin (LV) (250 mg/m<sup>2</sup>, i.v., d 15-16), recycled every 4 weeks, in a phase II study on 24 patients over 65 years. The RR was 50% with a disease control of 87.5% and mild toxicity. The median PFS and OS were 9 and 14 months, respectively [94]. The same combination regimens was tested in another phase II trial. In this regimen MITO was administered at the same dose, LV at the dose of 10 mg/m<sup>2</sup>, i.v., and 5-FU 350 mg/m<sup>2</sup>, i.v., both on day 1, 2 and 3 recycled every 4 weeks. A total of 27 patients were evaluable for activity with RR 22.2%, median TTP of 5.5 months and median OS of 14 months. The main toxicity was grade 3-4 neutropenia in 16.2% with 2 patients who developed a moderate cardiotoxicity [95]. Two trials investigated the combination

of MITO plus methotrexate in patients aged more than 70 years. The RR reported in the 2 trials was 39% and 50% with MDR of 6.8 and 6 months and a median OS of 9 and 8 months, respectively [96, 97].

TAX-based combination regimens have been investigated in elderly women also. O'Rourke *et al.* treated 39 elderly patients ( $\geq 65$  years) with TAX 100 mg/m<sup>2</sup> by 1-h infusion plus carboplatin AUC 2, on days 1, 8 and 15 every 4 weeks. The RR was 46% with a median OS of 13 months. Grade 3-4 neutropenia in 33% of cases and a grade 3-4 neuropathy in 18% of patients was reported [98].

Beex *et al.* treated 23 elderly patients ( $> 70$  years) using 100% (in 10 cases) and 75% (in 13 cases) of the standard dose of CMF regimen. Results were similar in both groups and superimposable to those commonly reported with standard CMF. These results seem to suggest that the CMF dose could not exceed 75% of the standard dose in the elderly [99]. Taylor *et al.* treated 181 patients over 65 years with either TAM or CMF in a randomised crossover study. Response rate was 45% with TAM and 38% with CMF, with MDR of 10.4 and 7.9 months, respectively. The Authors concluded that starting with hormonal therapy rather than CMF chemotherapy could be justified in elderly patients while polichemotherapy, however, is safe and active after hormonal treatment failure [100].

Bajetta *et al.* treated 73 women ( $\geq 70$  years) with doxifluridine (600 mg/m<sup>2</sup>/b.i.d., p.o., d 1, 2, 3, 4) and LV (25 mg/b.i.d., p.o., d 1, 2, 3, 4), both given orally, recycled every 12 days. The OR was 26% with MDR and OS of 7 and 24 months, respectively. The treatment was very well tolerated and side effects were manageable and always reversible [101].

In a phase I-II trial the combination of capecitabine (800-1250 mg/m<sup>2</sup>, p.o., from day 1 to 14) plus VNR (20-25 mg/m<sup>2</sup>, i.v., day 1 and 8) every 21 days, was administered to 36 elderly patients. The RR was 50% and the dose-limiting toxicity was mainly neutropenia [102]. In a randomised phase II trial, 18 patients aged more than 65 years were randomised to receive: arm A: capecitabine (1500 mg/m<sup>2</sup>, p.o., for 14 days); arm B: capecitabine at the same dose plus gemcitabine (GEM) (1000 mg/m<sup>2</sup>, i.v., day 1 and 8); arm C: capecitabine at the same dose plus VNR (25 mg/m<sup>2</sup>, i.v., day 1 and 8). All treatments recycled every 21 days and anastrozole was combined to chemotherapy for ER-positive patients. The preliminary results reported a RR of 12.5% in arm A, 50% in arm B and 33.3% in arm C. Each schedule was well tolerated [103]. Rozzi *et al.* in a phase II study administered to 30 elderly patients ( $\geq 70$  years) with ABC, VNR 25 mg/m<sup>2</sup>, i.v., on day 1 and 14 plus 5-FU 250 mg/m<sup>2</sup>, i.v., protracted infusion from day 1 to day 14, recycled every 4 weeks. The RR was 50%, median TTP was 4.4 and OS 12.1 months. Toxicity was mild with grade 3-4 neutropenia in 46%, grade 3 anemia in 20% and grade 3 thrombocytopenia in 17% of patients [104]. The combination of VNR (25 mg/m<sup>2</sup>, i.v., day 1 and 8) plus GEM (1000 mg/m<sup>2</sup>, i.v., day 1 and 8) every 3 weeks, was administered to 26 elderly patients ( $\geq 65$  years). The RR was 53.8% with a MDR for CR and PR of 7 and 10 months, respectively. Neutropenia in 5 (19.2%) cases, rapidly resolved with G-CSF administration, was the worst toxicity [105].

## NEW DIRECTIONS

Our literature review showed an increasing interest for oral drugs. In the future, novel biological agents should be an interesting new approach mainly in the elderly considering their low toxicity profile.

### Oral Drugs

Patient's preferences and quality of life issues, which are becoming central considerations in palliative chemotherapy, request the development of oral drugs administration. Indeed, some Authors suggested that i.v. lines were a major source of discomfort and stress for cancer patients and approximately 90% of them expressed a preference for oral versus i.v. chemotherapy, predominantly because of the convenience of administration outside a clinical setting or current concerns or previous problems with i.v. access [106]. For the above mentioned reasons, if equivalent safety and efficacy can be demonstrated, the oral drugs formulation could provide more convenience for patients; this added convenience may be particularly important in elderly and unfit patients. Anyway, the majority of drugs administered orally are intended to act systematically, and for these, absorption is a prerequisite for activity. Delays or losses of the drug during absorption may contribute to variability in the drug response, and occasionally, may result in the treatment failure. An ideal chemotherapeutic drug would have little interpatient variability in absorption and time curve (AUC) and, more importantly, little inpatient variability with successive doses [107]. Moreover, oral chemotherapy agents have drawn attention to age-related changes that may affect drug absorption, including less absorptive surfaces of the small bowel and splanchnic circulation, reduced gastric motility, and reduced gastric secretion [108].

In the present review, capecitabine is an interesting oral drug. It is a selectively tumor activated fluoropyrimidine which is effective in a wide range of solid tumors, particularly in breast and colon cancer. In 4 reported studies, single-agent capecitabine was active and well tolerated in the treatment of ABC elderly patients [78-81].

Based on the available data and our experience as well, VNR seems to be one of the most active single-agent.

Bonneterre *et al.* conducted a dose-finding phase I study in advanced breast cancer patients. Three dose levels were evaluated on a weekly regimen basis: 60, 80 and 100 mg/m<sup>2</sup>. Twenty-seven patients were enrolled in the study and the maximum tolerated dose was 100 mg/m<sup>2</sup> with a dose-limiting toxicities being neutropenia, nausea/vomiting and neuroconstipation. The recommended dose of oral VNR for further trials was defined at 80 mg/m<sup>2</sup>/week. The activity was observed at 80 and 100 mg/m<sup>2</sup> [109].

Following these results, the absolute bioavailability of oral VNR was determined in 24 patients receiving oral administration at 80 mg/m<sup>2</sup> or i.v. VNR at 25 mg/m<sup>2</sup> one week apart in a cross over design. The bioavailability factor calculated on blood exposure (AUC) was 43 ± 14%. When data from the population pharmacokinetic analysis is taken into account (including all the patients from phase I studies) the bioavailability factor is 36 ± 10% and this has formed the justification for a pragmatic use of about 40% as the basis for clinical equivalence studies. Based on these results the oral dose of 80 mg/m<sup>2</sup> was demonstrated to correspond to 30 mg/m<sup>2</sup> of the i.v. formulation and 60 mg/m<sup>2</sup> oral to 25 mg/m<sup>2</sup> i.v. [110]. Recently, a trial performed in elderly patients with advanced non small cell lung cancer, demonstrated that the pharmacokinetics of oral VNR is not altered in older patients who presented similar bioavailability and at least comparable inter-individual variability to younger patients [111]. Based on these data studies of oral VNR in ABC elderly patients are warranted.

### Targeted Therapies

The numerous molecular mechanisms implicated in the pathogenesis of breast cancer present exciting avenues for target-specific approaches to therapy. Any categorisation of these agents is difficult with overlap in several features. The Table 5 summarises the new biologic agents related their specific target and investigated in anticancer treatment. Based on the current data, the inhibitors of cell signalling seem to be the most promising class of agents for the treatment of breast cancer.

**Table 5. New Biological Agents Classification Related to their Generic and Specific Target**

Generic target	Specific target	Agent
Signal transduction	HER-2/neu EGFR RAS/RAF	Antibody anti HER-2/neu Antibodies anti EGFR and EGF-like EGFR tyrosine kinase inhibitors Farnesyl transferase inhibitors Antisense oligonucleotides
Neoangiogenesis	VEGF	Antibodies anti VEGF VEGF receptor tyrosin kinase inhibitors
Invasiveness and metastatic spread	Matrix metalloproteinases Adhesion molecules	Small molecule inhibitors Synthetic glycoamines analogues
Oncosuppression	P53	MDM2 antagonists
Apoptosis	COX-2	COX-2 inhibitors

EGFR = epidermal growth factor receptor; VEGF = vascular endothelial growth factor; COX-2 = cyclooxygenase.

HER-2/neu, a member of the group I growth factor receptor family, is a tyrosine-kinase membrane receptor that, when activated, induces a phosphorylation cascade in cytoplasmic kinases leading to increased transcription of nuclear proteins and cellular growth. It is amplified and/or overexpressed in 20% to 30% of patients with breast cancer [112]. Overexpression of this oncogene product is associated with increased rates of tumour growth, enhanced rates of metastasis, shorter DFS, and OS [112-114]. Patients with HER-2/neu-overexpressing tumours have more aggressive and more malignant courses. HER-2/neu has been targeted by monoclonal antibodies, immunoconjugates, vaccines, antibody-directed enzyme prodrug therapy, antisense therapy and gene therapy [115].

Trastuzumab is a humanized monoclonal antibody against the extracellular domain of HER-2/neu [116]. As a single agent, trastuzumab resulted in 15% objective response in ABC, as second-line treatment [117]. Trastuzumab is well tolerated, low-grade fever, chills, fatigue and constitutional symptoms occur primarily with the first infusion and serious adverse effects are infrequent [118]. Trastuzumab has been showed well tolerated in elderly women (> 60 years) with HER-2-positive ABC and produces significant benefits added to chemotherapy [118, 119].

The EGFR (Epidermal Growth Factor Receptor), another member of the group I growth factor receptor family, is a 170 kDa transmembrane glycoprotein that consists of an extracellular domain, a hydrophobic transmembrane domain and an intracellular region containing the tyrosine kinase domain. The EGFR exists as inactive monomer, which dimerizes after ligand activation. This causes homodimerization or heterodimerization between EGFR and another member of the erb receptor family. After the ligand binding, the tyrosine kinase intracellular domain of the receptor is activated, with autophosphorylation of the intracellular domain, which initiates a cascade of intracellular events. Several studies have demonstrated that EGFR-mediated signals also contribute to other processes that are crucial to cancer progression, including angiogenesis, metastatic spread, and inhibition of apoptosis [120].

Gefitinib (ZD1839, Iressa), a synthetic anilinoquinazoline, is a p.o. active, selective reversible inhibitor of EGFR tyrosine kinase. Although many ER-positive breast cancers initially respond to anti-hormones agents, responses are commonly incomplete with increasing resistance. Overexpression of EGFR is associated with the anti-hormone resistant phase of clinical disease. *In vitro* investigations, employing gefitinib, in MCF-7 breast cancer cells reported that increased EGFR signaling limited antiproliferative and proapoptotic activity of anti-hormones promoting resistance [121]. Recently, a phase II trials tested gefitinib in ABC patients. Robertson *et al.* treated with gefitinib 500 mg, 33 patients with either ER-negative or ER-positive breast cancer that became clinical resistant to tamoxifen. The median age was 61 years (range 32-85 years). The Authors reported a RR of 10.5% in 19 evaluable patients [122].

Overexpression of cyclooxygenase-2 (COX2) has been shown to be present in a varying but significant proportion of patients with breast cancer and it has been associated with significantly worse survival [123]. A phase II study, tested

the combination of exemestane, a steroidal aromatase inhibitor, plus a COX2 inhibitor, celecoxib, in 30 postmenopausal patients with ABC. Of 19 evaluable patients 6 (31%) reported a partial response with mild toxicity [124].

## CONCLUSIONS

The treatment of elderly patients is an emerging issue. Although 48% of breast cancer patients are 65 years old or older, these patients are severely underrepresented in breast cancer trials. A recent study tested whether older patients were offered trials significantly less often than younger patients and whether older patients who were offered trials were more likely to refuse participation than younger patients. This study reported that the greatest impediment to enrolling older women onto trials was the physicians' perceptions about age and tolerance of toxicity [125].

The question of which older women may benefit from adjuvant chemotherapy was addressed in a decision analysis. In fact, Extermann *et al.* calculated the threshold for the risk of relapse from breast cancer above which adjuvant chemotherapy would be beneficial. They found that the threshold varied with the age, functional status, and health status of the patient. For a 70-year-old woman in average health, adjuvant chemotherapy would be beneficial for her survival if her risk of relapse is 10% or higher and for an 80-year-old, when it is 21% or higher. This analysis was based on the assumption that the most of patients would accept adjuvant chemotherapy for a 1% or higher improvement of overall survival [4]. Guidelines and decision-making tools in early breast cancer were reviewed also in a recent article in which were described some aids that may be used to help inform women about their treatment [126]. Prospective adjuvant trials for elderly should include only those patients.

Adjuvant chemotherapy, preferably including an anthracycline especially in patients with HER-2/neu-positive tumours, seems to be beneficial in older women who have substantial risk of dying of breast cancer. It is widely believed that the incidence and severity of toxic effects from anthracyclines are greater in older patients than in younger ones, and clinical experience often reinforces this belief. Anyway, Ibrahim *et al.* confirmed the possibility to administer anthracyclines in elderly women with breast cancer. They performed a retrospective analysis on 390 women aged 65 years or older treated with doxorubicin-based adjuvant chemotherapy. Of these group 65 were aged 65 years or older. The DFS and OS rates reported in elderly patients were similar to those seen in younger patients [127]. Moreover, new microarray data may indicate the women at high risk of recurrence for which adjuvant chemotherapy is indicate [128].

Regarding ABC, unfortunately, among the published studies, one only is a randomised phase III trial while several phase II trials have been performed. The most part of the studies enrolled elderly patients with a cut-off age ranging from 60 to 65 years old, probably not representative of real elderly population. Many referenced studies included in the same series patients treated as first-, second- and third-line chemotherapy confounding the reported results. Some of the cited trials used anthracycline-based chemotherapy. Ibrahim *et al.* analysed retrospectively 1011 women with

ABC over 65 years (24%) or 50-64 years, all treated with a doxorubicin-based chemotherapy. Although OR was higher for the younger patients (67% versus 51%,  $p = 0.001$ ), no significant difference in terms of dose-intensity, TTP, OS and toxicity was observed [129]. The correlation between aging and doxorubicin-induced congestive heart failure in elderly patients with ABC was studied, retrospectively, in 682 patients aged 50 years or older of which 144 were 65 years old or more. Older patients with no significant comorbidity could be treated with doxorubicin-based chemotherapy with no added risk of developing congestive heart failure beyond that in the younger age group [130]. While the response to chemotherapy and clinical outcome are certainly poorer in elderly patients with chronic comorbidity than in younger and healthier patients, the evidence to date suggests that the benefits and toxic effects of chemotherapy in otherwise-healthy older patients are comparable to those in younger ones. Based on the described studies, single-agent chemotherapy seems to determine superimposable results as compared to polichemotherapy. To date even if there is no specifically randomised study, single-agent chemotherapy probably might be considered a reasonable choice of treatment for ABC in the elderly.

The role of liposomal anthracyclines, that seems appealing in elderly patients, is still to be determined.

Great interest is for oral drugs if well tolerated and usually with a good patient's compliance. One of the main research-line is to explore the role of targeted therapies considering their excellent toxicity profile. The CGA can assist in determining the treatment or care plan that is most appropriate in according to the patient's functional status, social circumstances and life expectancy. Older patients may also be more susceptible to toxicity therefore, the guidelines for managing toxic effects, such as neutropenia and anaemia, can be used to help maintain the dose intensity of chemotherapy producing optimal outcomes.

In conclusion, chemotherapy is feasible and active whether in early breast cancer than in ABC elderly patients resistant to hormonal therapy or with visceral metastases. Considering that breast cancer is a disease of older women, the population of developed countries is not getting any younger, and the most part of these patients need to be treated with chemotherapy, we must increase accrual of older women to clinical trials in general, especially to large randomised phase III studies, including quality of life evaluation.

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