

Chemotherapy in elderly patients with advanced breast cancer

Review Article

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Summary

Breast cancer arises in about 48% of patients older than 65 years and more than 30% occurs in those over 70 years. Chemotherapy is administered to elderly patients with advanced breast cancer resistant to hormonal treatment or with visceral metastases. 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. One of the main field of clinical research is the role of new biological agents. In order to plan medical treatment in advanced breast cancer elderly patients, and to further individualise treatment choice, is mandatory to practice a comprehensive geriatric assessment that includes assessment of comorbidity, socio-economic conditions, functional dependence, emotional and cognitive conditions, an estimate of life expectancy and recognition of frailty. (The authors review the literature regarding age-specific issues in the management of advanced breast cancer elderly patients, and report their own experience in the field.)

I. Introduction

Ongoing epidemiologic research over the past several decades has consistently confirmed a continuing trend toward an aging population. The over-65 age group is growing faster than other age groups, and therefore accounts for an increasing percentage of the total population. The portion of the population older than 65 rose from approximately 8% in 1950 to 13% in 1990. By the year 2030, fully 20% of the population will be older than 65 (Yancik, and Lies 2000). 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 (Klimmick and Balducci 2000). Breast cancer in the elderly has attracted considerable interest in the recent years. Data from the Surveillance, Epidemiology and End Results (SEER)

Program show an increase of patients diagnosed with breast cancer and having 65 years or older from 37% in 1973 to 46.7% in 1995 (Surveillance, Epidemiology and End Results (SEER) Program 1998). 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 (Levi et al 2001).

Chemotherapy is indicated in elderly patients with advanced breast cancer 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 (Busch et al 1996). 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 advanced breast cancer (ABC) frequently suffer from tumour-related symptoms and need some kind of palliative treatments. In clinical practice, they often receive inadequate and untested treatments (Fentiman et al 1990; Monfardini and Yancik 1993).

This article explores age-specific issues of the management of ABC in older women, and the authors report their own experience in this setting.

II. 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 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 (Surveillance, Epidemiology and End Results (SEER) Program 1998). Furthermore we must consider that is very difficult to establish a maximum age for chemotherapy treatment 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 (Balducci 2000).

III. Comorbidities and frailty

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 comorbidity 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 (Surveillance, Epidemiology and End Results (SEER) Program 1998). Comorbidities are serious medical conditions that are not directly related to the cancer itself but involve the cardiovascular system, the respiratory

system, the renal or hepatic system, and any other major organ system. These conditions are usually chronic rather than self-limiting or acute and easily treated. Comorbidity, like impaired functional status, is a key negative prognostic factor in elderly patients with cancer and it can also adversely affect the patient's functional status.

Another important issue is the definition of frail elderly persons. 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 (Balducci and Stanta 2000; Balducci and Exterman 2000).

The frailty is a condition in which most functional reserve is exhausted. Frail patients are those who depend on others for the activities of daily living prevalently because of physical and cognitive dysfunction. 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 comorbidity has not been defined (Yancik et al 2001). 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 (Litchman and Villani 2000).

In order to plan medical treatment in ABC elderly patients, and to further individualise treatment choice, is mandatory to practice 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. The choice of the drug should be based on the evaluation of both toxicity profile of each drug and on the CGA of the patient. The basic component of CGA are presented in **Table 1** (Balducci et al 2001).

IV. Literature review

All published papers specifically addressing chemotherapy of elderly ABC patients until March 31, 2003 were searched using MEDLINE (PubMed, National Library of Medicine, Bethesda, MD, USA; used keywords: advanced breast cancer, elderly patients, chemotherapy). Therefore, all published papers in medical journals were reviewed and all abstracts presented at the last 5 years main international meetings were considered.

Our literature search found 25 studies. Twelve of them have been published as abstract at main international meetings and 13 have been published as extended papers. One trial only was a phase III randomised study.

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

The **Table 2 and 3** summarised the results of single-agent and combination chemotherapy, respectively.

A. Single-agent chemotherapy

Sixteen trials of single-agent chemotherapy were reported. Three trials used single-agent oral idarubicin (IDA). Chevalier et al (1990) on 30 elderly patients (> 70 years) with ABC using m^2 IDA (15 mg/m², 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. Provè et al (1998) treated 29 elderly patients failing hormonal therapy with IDA (20 mg/m²/week x 4). The Authors reported a RR of 24% with MDR of 8.5 months and mild toxicity consisting, mainly of myelosuppression. Toffoli et al (2000) used IDA on 10 elderly patients, at the dose of 5 mg/day and 10 mg/day every other day, for 21 days, recycled every 4 weeks. A RR of 20% was reported with severe toxicity and the Authors suggested a safer dosage of 5 mg/day for further experiences.

Another trial by Chevalier et al (1992) using single-agent pirarubicin (30 mg/m², i.v., d 1, every 3 weeks) on 31 elderly patients reported 25% RR with a median time to progression (TTP) of 3 months.

Repetto et al, (1995) using mitoxantrone (MITO) (10-14 mg/m², i.v., d 1 every 3 weeks), reported 26% PR

among 27 patients aged ≥ 68 years; MDR and OS were 6 and 8 months, respectively.

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/m²) 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/m² and over, every 21 days, is too toxic in the elderly (Zanetta et al 2000). On the contrary, Constenia et al (1999) treated 14 elderly patients (> 65 years, six of which frail) with TXT at 75 mg/m² and 100 mg/m², every 3 weeks, with lenograstim support. They reported a RR of 71% with acceptable hematological toxicity. Two trials used weekly TXT. D'hondt et al (2000) administered weekly TXT at the dose of 36 mg/m² 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. In another phase II study, TXT (36 mg/m²) 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 occurring in 20% of patients (Hainsworth et al 2001).

Table 2. Phase II studies with single agent chemotherapy

Author	No.pts	Age (years)	Drug	RR (%)	MTP (mos)
Chevallier, 1990	31	> 70	Idarubicin	26	2.7
Provè, 1998	29	> 65	Idarubicin	24	8.5
Toffoli, 2000	10	> 65	Idarubicin	20	-
Chevallier, 1992	30	> 70	Pirarubicin	25	3
Repetto, 1995	27	> 68	Mitoxantrone	26	6
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
Repetto, 2002	29	> 70	Paclitaxel	55	-
O'Shaughnessy, 1998	62	> 55	Capecitabine	25	-
	33		Vs CMF	16	-
Procopio, 2001	31	> 65	Capecitabine	35	-
Sorio, 1997	25	> 65	Vinorelbine	30	-
Buonadonna, 1998	38	> 65	Vinorelbine	39.5	7
Vogel, 1999	56	> 60	Vinorelbine	38	6
Rossi, 2003	24	> 70	Vinorelbine	37.5	5

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

Table 3. Studies with combination chemotherapy

Author	Phase	No.pts	Age (years)	Drug	RR (%)	MTP (mos)
Zaniboni, 1998	II	39	72*	Idarubicin + Cyclophosphamide	37.2	-
Kurtz, 2000	I	19	≥ 65	Idarubicin + Cyclophosphamide	21	6.6
Gladieff, 1996	II	25	> 70	Mitoxantrone + vinorelbine	22	13
Mammoliti, 1996	II	24	> 65	Mitoxantrone + Levo-leucovorin + 5-fluorouracil	50	9
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	≥ 65	Paclitaxel + carboplatin	46	-
Taylor, 1986	III	181	> 65	Tamoxifen	45	10.4
				Vs CMF	38	7.9

RR = response rate; MTP = median time to progression; CMF = cyclophosphamide, methotrexate, 5-fluorouracil; *median age

Paclitaxel (TAX) was administered weekly (80 mg/m², i.v. day 1, 8 and 15 every 4 weeks), in a phase II study, 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 (Repetto et al 2002).

Two studies with capecitabine were reported. O'Shaughnessy et al randomised patients in a phase II trial to capecitabine (2510 mg/m²/b.i.d., p.o., days 1 to 14, every 3 weeks) or CMF (cyclophosphamide, methotrexate and 5-fluorouracil). 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 (O'Shaughnessy et al 1998). Procopio et al (2001) treated 40 women older than 65 years with capecitabine (2500 and then 2000 mg/m²/b.i.d., p.o., day 1 to 14, every 3 weeks). They reported RR of 35% with a median TTP of 6 months, one patient died due to gastrointestinal toxicity among 31 evaluable patients.

Four studies reported on single-agent vinorelbine (VNR) in the treatment of elderly patients with ABC (Sorio et al 1997; Buonadonna et al 1998; Vogel et al 1999; Rossi et al 2003). Sorio et al (1997) treated 20 patients (> 65 years) with VNR at the dose of 30 mg/m², i.v., as first-, second- and third-line therapy, on days 1 and 8 every 3 weeks, reporting 30% OR. Buonadonna et al (1998) reported 39.5% RR with MDR of 7 months and a disease control of 60.5%. The schedule of VNR used was 25 mg/m², on days 1 and 8, every 3 weeks. Median age was 70 years and about 40% of patients were treated as second-line therapy. Vogel et al (1999) 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/m², weekly for the first 13 weeks and then every 2 weeks. Median dose intensity of VNR was 20.6 mg/m²/week. Recently, Rossi et al (2003), treated 24 elderly ABC patients with VNR 30 mg/m², i.v. day 1 and 8, every 3 weeks. Nine (37.5%) objective responses (2 complete and 7 partial responses) were observed with MDR and survival 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.

B. Combination regimens

Among polichemotherapy trials, 2 included treatment with anthracyclines. Zaniboni et al (1998) 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. Kurtz et al performed a phase I trial using a fixed dose of CTX (200 mg/m²/day, p.o., d 1, 2, 3) and an increasing dose of IDA (10 mg/m²/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/m²/day. Among 14 patients, 4 (21%) achieved a PR with MDR of 6.6 months (Kurtz et al 2000).

Gladiett et al (1996) in a phase II study, treated 25 women older than 70 years with the combination of MITO (10 mg/m², i.v., d 1) plus VNR (20 mg/m², 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. Mammoliti et al (1996) used a combination of MITO (10 mg/m², i.v., d 1), 5-fluorouracil (500 mg/m², i.v., d 15-16) and levo-leucovorin (LV) (250 mg/m², 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. 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 (van Veelen et al 1998. Jagiello-Gruszfeld et al 2002).

TAX-based combination regimens have been investigated in elderly women also. O'Rourke et al (2002) treated 39 elderly patients (\geq 65 years) with TAX 100 mg/m² 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.

Beex et al (1992) 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. Taylor et al treated 181 patients over 65 years with either tamoxifen or CMF in a randomised crossover study. Response rate was 45% with tamoxifen 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 (Taylor 4th et al 1986).

Bajetta et al (1998) treated 73 women (\geq 70 years) with doxifluridine (600 mg/m²/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.

V. New Directions

Our literature review showed an increasing interest for oral drugs. In 8 out of the 25 reported studies the Authors used an oral drug formulation. In the future novel biological agents should be an interesting new approach. The use of oral drugs in this setting as well is of great interest.

A. Oral drugs

Patient's preferences and quality of life issues, which are becoming central considerations in palliative treatment regimens, request the development of oral drugs administration. Indeed, a work has 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 (Liu et al 1997). For the mentioned reasons, if equivalent safety and efficacy can be demonstrated, the oral drugs formulation provides 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 (DeMario and Ratain 1998).

In the present review, capecitabine is an interesting oral drug. Capecitabine is a selectively tumor activated fluoropyrimidine which is effective in a wide range of solid tumors, particularly in breast and colon cancer. In the two reported studies, capecitabine was active and well tolerated in the treatment of ABC elderly patients (O'Shaughnessy et al 1998; Procopio et al 2001).

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

Bonnetterre 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/m². Twenty-seven patients were enrolled in the study and the maximum tolerated dose was 100 mg/m² 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/m²/week. The activity was observed at 80 and 100 mg/m² (Bonnetterre et al 1996).

Following these results, the absolute bioavailability of oral VNR was determined in 24 patients receiving oral administration at 80 mg/m² or i.v. VNR at 25 mg/m² 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/m² was demonstrated to correspond to 30 mg/m² of the i.v. formulation and 60 mg/m² oral to 25 mg/m² i.v. (Marty et al 2001). 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 (Puozzo et al 2001). Based on these data studies of oral VNR in ABC elderly patients are warranted.

B. New biological agents

The numerous molecular mechanisms implicated in the pathogenesis of breast cancer present exciting avenues for target-specific approaches to therapy. 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.

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 (Press et al 1990). Overexpression of this oncogene product is associated with increased rates of tumour growth, enhanced rates of metastasis, shorter disease-free survival, and overall survival (Slamon et al 1989; Press et al 1990; Liu et al 1995). 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 (Hortobagyi 1990).

Trastuzumab is a humanized monoclonal antibody against the extracellular domain of HER-2/neu (Hudziak et al 1989). As a single agent, trastuzumab resulted in 15% objective response in ABC, as second-line treatment (Cobleigh et al 1999). Trastuzumab is well tolerated, low-grade fever, chills, fatigue and constitutional symptoms occur primarily with the first infusion and serious adverse effects are infrequent (Hortobagyi 1999). Trastuzumab has been showed well tolerated in elderly women (> 60 years) with HER-2-positive ABC and produces significant benefits added to chemotherapy (Fyfe et al 2001).

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 monomers, which dimerize 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 (Ciardiello and Tortora 2001).

ZD1839, a synthetic anilinoquinazoline, is a p.o.

active, selective reversible inhibitor of EGFR tyrosine kinase. Recently, 2 phase II trials tested ZD1839 in ABC patients. Robertson et al (2002) treated with ZD1839 500 mg, 22 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 partial response in 9% of patients. Albain et al, (2002) treated with an oral daily 500 mg dose of ZD1839 until disease progression, intolerable disease or consent withdrawal, 63 pretreated ABC patients (ages 34-80 years) with interesting results. The use of oral drugs as well among new biological agents is of great interest.

VI. Conclusions

The treatment of elderly patients is an emerging issue. 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. 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 ABC. They performed a retrospective analysis on 1011 women 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 (Ibrahim et al 1996). 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 patients. Age is not predictive of treatment failure and chemotherapy is not necessarily less effective or less tolerable in older patients.

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 the standard treatment for ABC in the elderly.

Great interest is for oral drugs if well tolerated and usually with a good patient's compliance.

One of the main research-line to explore is the introduction of new biological agents in the treatment schemes. In fact, if new biological agents proved to be effective in the treatment of ABC, therapeutic strategies in the elderly could include a very useful tool, considered their excellent toxicity profile, very suitable for this

peculiar patient population.

In conclusion, chemotherapy is feasible and active in ABC elderly patients resistant to hormonal therapy or with visceral metastases. Considering that the most part of these patients need to be treated with chemotherapy, large randomised phase III trials, including quality of life evaluation, are warranted.

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