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Review

Cytotoxic therapy for the elderly with metastatic breast cancer: A review on safety, pharmacokinetics and efficacy

P. Hamberg, J. Verweij, C. Seynaeve*

Department of Medical Oncology, Erasmus University Medical Center, Daniel den Hoed Cancer Center, P.O. Box 5201, 3008 AE Rotterdam, Rotterdam, The Netherlands

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ABSTRACT

As the incidence of invasive breast cancer, mainly developing at older age, is rising, the absolute number of elderly developing metastatic disease is also increasing. In view of improved life expectancy, sociocultural changes and better supportive measures for chemotherapy-induced toxicity, there is an increasing request for the administration of chemotherapy in elderly. At the moment, medical oncologists are still reluctant to use chemotherapy in elderly partly because of concern about increased toxicity and poor tolerability of this patient cohort, and the inability to appropriately select elderly that may benefit from chemotherapy. The question is whether this attitude remains justified.

In this review, the current status of clinical research in the area of metastatic breast cancer regarding toxicity and activity of chemotherapy in older breast cancer patients is discussed. Further, data on pharmacokinetics are emphasised as age-related physiologic changes may affect these features with consequences for toxicity and decision-making. Moreover, data on assessment tools trying to characterise the 'functional age' are reviewed.

In general, the literature data are scarce and hampered by major limitations, while pharmocokinetic data indicate that a different approach in older breast cancer patients does not always seem justified. To increase our knowledge aiming at optimisation of cancer treatment in elderly, there is a clear necessity for prospective, well-designed studies with emphasis on the particular requirements of older patients and incorporation of pharmacokinetic and -dynamic evaluation of cytotoxic agents used in this specific group. As in other research areas, maximal progress will be achieved by joined efforts of co-operative research groups.

1. Introduction

Breast cancer (BC) remains the most common type of invasive cancer in females in nearly all developed countries, showing an increased incidence over the last decades.[1] The estimated number of new patients in 2006 for Europe and the US are 370.100 and 212.900, respectively.[1,2] The probability of developing invasive BC increases with advancing age.[1] Currently, more than half of all breast cancer cases in the western world occur in women of 65 years and older. While the total European population will slightly decrease in the next decades, there will be a parallel demographic shift towards an in-

* *Corresponding author:* Tel.: +31 10 4391754; fax: +31 10 4391003.
E-mail address: a.hamberg@erasmusmc.nl (P. Hamberg).
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creased percentage of elderly[3] resulting in a higher number of elderly with (metastatic) BC. Although metastatic breast cancer (MBC) remains an incurable entity, in up to 10% of the patients, survival extends to 10 years or longer,[4] indicating the need for effective systemic therapy, also in older patients. The available and newer therapeutic options aim at providing symptom palliation by control of disease progression with preservation of quality of life, and prolongation of survival. Palliative chemotherapy for MBC might be considered in elderly with hormone receptor negative tumours, progressive disease refractory to endocrine therapy, visceral disease or fast growing/life threatening disease.

2. Age-related characteristics of patients and their tumours

It is important to try to define 'elderly' and to determine whether elderly or tumours affecting elderly are different compared to their younger counterparts. There is no commonly accepted cutoff age that classifies 'elderly'. However, in the underneath, data are given showing that physicians start to treat patients differently from the age of 65 years onward. In all of the further discussions one will have to take into account that physiological age may be more important than calendar age, and that thus the individual patient could be approached differently as compared to what is considered standard for the age group.

Patient age at BC diagnosis has a significant impact on the biomarker profile reflecting a specific tumour biology, most relevantly yielding a larger proportion of ER-positive and EGFR/Her2Neu negative tumours in older patients.[5,6] Despite this less aggressive tumour profile, older women more likely are diagnosed at a further advanced BC stage, and their risk of receiving less than 'optimal' treatment is higher.[7,8] So, a relatively large proportion of these patients will ultimately develop metastatic disease. Furthermore, it is important to recognise that by achieving older age, healthy persons have a longer expected total lifetime than the general population at birth (Table 1). For healthy women of 65 years of age, the further life expectancy is another 19.5 years.[9,10]

Regarding the administration of systemic therapy, awareness of age-related physiologic changes is important because of a potential impact on pharmacokinetic and -dynamic characteristics.[11] These alterations may influence the choice for a particular chemotherapy regimen, compared to the therapy that is commonly administered to younger patients. The most prominent physiological changes relevant to chemotherapy are altered body composition, decreased absorption from the gastro-intestinal system, decreased glomerular filtration rate, altered drug metabolism in the liver, lower bone marrow cellularity, lower cardiac output, diminished organ perfusion and a decline in neurological performances.[12]

Further, polypharmacy is more common in older patients. Cancer patients older then 65 years use an average of 4.4 different medications a day. In this respect, the data from a survey indicating that 47% of the patients were taking over the counter drugs without reporting them are very relevant.[13] Since the risk of non-compliance, as well as the risk of drug–drug interactions is strongly correlated by the number of medications used, this especially may be of importance in older patients.[13]

Table 1 – Life expectations of healthy females by age

Age	Females (US)[9]	Age cohort	Females (The Netherlands)[10]
65	19.8	65–69	19.3
70	16.0	70–74	15.4
75	12.6	75–79	11.7
80	9.6	80–84	8.5
85	7.2	85–89	6.0
90	5.2	90–94	4.1
95	3.7	95–99	2.8

3. Patient and physician perceptions

Decisions concerning the initiation of chemotherapy for MBC are mainly driven by the balance between efficacy and toxicity. Knowledge of factors determining this balance is crucial, in order to assess the impact of increasing age. Pharmacokinetic and -dynamic data of cytotoxic anti-tumour agents in elderly can be helpful in this respect. To reach a balanced decision, some major issues should be considered. Are elderly willing to accept chemotherapy? How to appropriately select the individual elderly for chemotherapy by balancing the benefits and toxicities? Which chemotherapy regimen(s) should or can be administered in the elderly with MBC?

Extermann et al., reported that the willingness to receive chemotherapy of patients older than 70 years is high, being 71–78% for toxic chemotherapy such as a platinum/taxane-based combination, and 89–100% for milder chemotherapy (e.g. a weekly vinorelbine-containing regimen).[14]

However, the second question is more difficult to answer. Chronological age does not automatically reflect the functional reserve or frailty of a patient. It is known that the prevalence of co-morbidity, and therefore co-medication, in patients is increasing with age, being 28% in the age group of 50–64 years and 67% in patients older then 80 years.[15] In this respect, it is of interest that from all cancer patients, the lowest prevalence of co-morbidity was observed among breast cancer patients.[15] In a French survey among oncologists, 35% expressed that they would treat patients between 65 and 74 years of age differently, compared to a patient 55 years of age. This was even 62% for the group of patients older than 75 years. The most important criterion for this decision was the subjective evaluation by the physician of the general health status of the patient.[16] In general, oncologists use the Karnofsky Performance Scale (KPS) or ECOG performance scale to assess the overall functional status of a patient. This type of performance assessment, however, can be misleading in the older patient, because clinical trials relying on these scales have largely excluded the frail elderly. Indeed, overestimation of the functional status of the elderly hereby is a known problem.[17] Comprehensive geriatric assessment (CGA) as well as other tools have been studied trying to assess the frailty of patients. However, in clinical practice only 2% of the oncologists collaborate on a regular basis with a geriatrician, a minority (12%) performs some kind of geriatric assessment,

while 59% of the oncologists never use any tool before proposing adjuvant chemotherapy.[18] Further, evidence that a CGA is predictive of activity or toxicity is hardly available.[19–21] In a recently published study in elderly with advanced ovarian cancer having relatively few geriatric conditions, it was found that dependence (meaning living with medical assistance in a specialised institution), depression and a poor performance status, were associated with more frequently severe toxicity of cytotoxic therapy. Overall survival was significantly affected by tumour stage, depression and the use of more than six different co-medications per day.[22] In a pilot study, it was demonstrated that a predictive risk index taking into account patient-related as well as chemotherapy-regimen-related variables is worthwhile exploring.[23] Recently, the task force on CGA of the International Society of Geriatric Oncology recommended that as long as there are no tools specifically tested in the older cancer patient, a general geriatric screening test should be used, to be extended with a more complete geriatric evaluation if the first screening is indicative for an increased risk of toxicity. By acknowledging the lack of evidence, however, the task force indicated that these recommendations should not yet be seen as a guideline.[24]

4. Considerations on adjuvant chemotherapy in elderly patients

Given the paucity of data on the tolerance of chemotherapy in elderly with MBC, data from the adjuvant setting may be of interest. Still, older women are less likely to receive adjuvant chemotherapy, even after adjustment of confounders related to tumour characteristics.[25] Also, it has been reported that the risk of toxicity associated with adjuvant chemotherapy for breast cancer patients older than 65 years depends on the type of administered treatment (CMF, anthracyclines or taxanes) rather than on the chronological patient age or co-morbidity.[26] While, certainly with dose-dense chemotherapy,[27] there is an increase in the occurrence of neutropaenia in elderly patients compared to younger patients,[27,28] non-heamatological toxicity seems to be either quite similar,[26–30] or increased.[31] In contrast, there may be less nausea and/or vomiting at increasing age.[32,33] Despite possibly increased toxicity, the quality of life of older women receiving adjuvant chemotherapy was found to be not worse than of younger women.[28,31] In view of this, and given the fact that the benefit of adjuvant therapy is mainly depending on the estimated risk of relapse, there is a trend towards a more frequent use of adjuvant chemotherapy in elderly BC patients.[34–37] However, we should keep in mind that the absence of tumour burden and disease-related symptoms provide patients receiving adjuvant chemotherapy with a more favourable baseline position to endure chemotherapy than patients with metastatic disease. Therefore, data from adjuvant chemotherapy cannot simply be projected to patients with MBC.

5. Chemotherapy for metastatic disease

Regarding following paragraphs, it should be kept in mind that most of the available data adressing the efficacy and toxicity of chemotherapy in elderly patients with MBC are derived from phases I and II studies of limited sample size, or retrospective subset analysis from randomised trials, having known limitations. Further, quite likely inclusion bias has occurred hereby, namely by only including the relatively healthy subset of elderly patients in accordance with the eligibility criteria of the studies. That this is indeed the case is reflected by the observation that the large majority (70–100%) of the population in all studies had a WHO performance status (WHO PS) of 0 or 1, which is not usually seen/expected in a 'real' cohort of the elderly.

6. Single agent chemotherapy (Table 2)

6.1. *Anthracyclines and anthracendiones*

Doxorubicin has not separately been studied as single agent in elderly with MBC. Age was not associated with an altered doxorubicin clearance in a small study on elderly patients,[38] while in a larger study simulating the pharmacokinetics (based on data from older studies) a decreased clearance of doxorubicin was found[39] (Table 3). As cardiotoxicity is one of the classical and most burdensome toxicities of anthracyclines, this is especially of concern in the elderly. However, data on the cardiotoxicity of single agent doxorubicin are not available (see Section 7.2). In general, the pegylated liposomal formulation of doxorubicin (PEG doxorubicin) is less cardiotoxic than doxorubicin,[40] and this also appears to apply to the elderly.[41] Even so, the incidence of cardiotoxicity due to PEG doxorubicin was comparable in MBC patients $\geqslant$70 years of age and in younger patients.[41] In a joined retrospective analysis of two studies, the anti-tumour activity of PEG doxorubicin was not affected by age, although the toxicity of this drug administered at a dose of 60 mg/m^2 in a 6 weekly regimen appeared to be more toxic in the elderly ($\geqslant$70 years). No difference in toxicity between different age cohorts was found if PEG doxorubicin was given at a dose of 50 mg/m^2, repeated every 4 weeks.[41]

Epirubicin, studied in a weekly regimen, which in younger patients is not standardly used, yielded anti-tumour activity with an acceptable toxicity profile.[42] But while the epirubicin clearance in multi-agent regimens was decreased in the elderly women[43] (Table 3), there are no data on pharmacokinetics of single agent epirubicin in the elderly.

Although the more convenient oral administration is attractive to patients, idarubicin is hardly used in breast cancer. Studying this drug at different dose levels in small groups of patients, a dose dependent, sometimes very severe toxicity (including toxic deaths) in elderly with MBC was observed.[44–46] Unfortunately, an applied multi-dimensional geriatric assessment failed to predict this outcome, possibly partly due to the small sample size.[46] The area under the curve (AUC) of idarubicin and idarubicinol (the principal metabolite of idarubicin) did not correlate with age,[47] but in patients experiencing grades 3–4 neutropaenia significantly higher idarubicin and idarubicinol levels were found in comparison to patients experiencing $\leqslant$grade 2 neutropaenia.[44] No correlation between plasma levels and response was found[44] (Table 3).

The applicability of mitoxantrone in elderly, despite relevant anti-tumour activity,[48,49] is limited by neutropaenia.[48] Furthermore, a general decrease in bone marrow cellularity,

Table 2 – Studies on single agent cytotoxic therapy in elderly women with metastatic breast cancer

Cytotoxic agent	Ref.	Dosage	Interval	*N*	Age (years)	Previous cytotoxic therapy	Neutropaenia grades 3–4	Other grades 3–4 toxicity[a]	Toxic death	PR or CR	SD
Pegylated Liposomal Doxorubicin	[41]	60–70 mg/m^2	q 6w	34	⩾70	Adjuvant 15%[b] Metastatic 15%[b]	58%	Stomatitis 50% Asthenia 15% Febrile neutropaenia 12% Anorexia 9% Anaemia 6% Thrombocytopaenia 6%	None	39%[b]	53%[b]
Pegylated Liposomal Doxorubicin	[41]	50 mg/m^2	q 4w	28	⩾70	See above	29%	Stomatitis 14% HFS 11% Asthenia 7% Nausea 7% Skin-toxicity 7%	None	See above	See above
Epirubicin	[42]	25 mg/m^2	q 7d	25 (8 BC; 17 other)	>74	NA	0%	–	None	43%	43%
Idarubicin	[44]	7.5 mg/day	d 1–21 q 28d	14	⩾65	NA	78%	Thrombocytopaenia 14% N/V 14% Diarrhea 14% Mucositis 14% Anaemia 7%	1	7 %	29%
	[44]	5 mg/day	d 1–21 q 28d	33	⩾65	NA	12%	–	None	21%	33%
	[45]	15 mg/m^2	d 1–3 q 21d	27 (112 cycles)	>70	Adjuvant 0% Metastatic 0%	27%	Thrombocytopaenia 12% N/V 9%[c]	None	26%	33%
	[46]	20 mg/m^2	q 7d	26	>70	Adjuvant 12% Metastatic 0%	42%	Asthenia 23% Dyspnoea 15% Confusion 12%	3	5%	26%
Mitoxantrone	[49]	10–14 mg/m^2	q 21d	27	>67	Adjuvant 11% Metastatic 0%	4% (leukopaenia)	–	None (of 1 death)	26%	39%
	[48]	8–14 mg/m^2	q 21d	13	>70	Adjuvant 15% Metastatic 0%	36% (75% at 14 mg/m^2 being DLT)	Thrombocytopaenia 9%	None	58%	33%
Paclitaxel	[50]	80 mg/m^2	q 7d	73	⩾65	Adjuvant 11% Metastatic 0%	15%	Anaemia 11% Asthenia 5%	None	20%	50%
	[52]	80 mg/m^2	d 1,8,15 q 28d	46	⩾70	Adjuvant 50% Metastatic 0%	9%	Cardiovascular 9%	2	54%	27%
	[51]	80 mg/m^2	d 1,8,15 q 28d	26	⩾70	Adjuvant 4% Metastatic 0%	12%	Anaemia 12%	None	43%	39%
	[54]	60–80 mg/m^2	d 1,8,15 q 28d	12	⩾70	33%	8%	–	None	42%	17%
	[53]	80 mg/m^2	d 1,8,15 q 28d	8	⩾70	NA	13%	Skin toxicity 13%	None	NA	NA
Docetaxel	[55]	36 mg/m^2	q 7d[d]	11	⩾70	Adjuvant 36% Metastatic 79%[e]	9%	–	None	40%	10%

(*continued on next page*)

Table 2 – *continued*

Cytotoxic agent	Ref.	Dosage	Interval	N	Age (years)	Previous cytotoxic therapy	Neutropaenia grades 3–4	Other grades 3–4 toxicity[a]	Toxic death	PR or CR	SD
	[56]	36 mg/m^2	d 1,8,15, 22,29,36 q 49d	41	⩾65[f]	Adjuvant 34% Metastatic 25%	4% (leuko-paenia)	Fatigue 20% Diarrhea 10% N/V 7% Peripheral edema 7%	None	36%	36%
	[57]	35 mg/m^2	d 1,8,15, 22,29,36 q 49d	21	⩾70	Adjuvant 67% Metastatic 0%	5%	Asthenia 10% Tearing 5%	None	33%	14%
	[64]	25–30 mg/m^2 40–50 mg/m^2 75–100 mg/m^2	q 7d q 14d q 21d or q 28d	8 19 10	⩾65	94%	14%	Asthenia 22 % N/V 8% Anaemia 5%	None	24%	42%.
Vinorelbine	[67]	30 mg/m^2	d 1,8 q 21d	25	⩾65	52%	36%	Constipation 12%	None	30%	NA
	[69]	30 mg/m^2	q 7d	56	⩾60	27%	80%	N/V 10% Anaemia 7% Asthenia 7% Pain 7%	1 (of 3 deaths)	40%	40%
	[72]	30 mg/m^2	d 1,8 q 21d	24	⩾70	Adjuvant 33% Metastatic 0%	25%	–	None	38%	33%
Capecitabine	[76]	1250 mg/m^2	Bidaily, d 1–14 q 21d	30	⩾65	Adjuvant 23% Metastatic 7%	0%	Diarrhea 13% Dyspnoea 10% N/V10% Fatigue 7%	2	33%	37%
		1000 mg/m^2	Bidaily, d 1–14 q 21d	43	⩾65	Adjuvant 19% Metastatic 7%	2%	Fatigue 12% Dyspnoea 5% N/V5%	1	47%	35%
UFT	[77]	150 mg/m^2	Bidaily, d 1–21 q 21d	10	⩾65	Adjuvant 60% Metastatic 30%	0%	Diarrhea 40% N/V 30% Fatigue 30% Thrombocytopaenia 20% Dehydration 20% Anorexia 10% Hypokalemia 10%	None	13%	50%
Doxifluridine	[78]	600 mg/m^2	Bidaily, d 1–4 q 21d	73	⩾70	Adjuvant 67% Metastatic 0%	0%	Diarrhea 22%	None	26%	12%

Ref: reference. q: every, w: weeks, d: days, N/V: nausea/vomiting, PR: partial response, CR: complete respons, SD: stable disease, BC: breast cancer, DLT: dose limiting toxicity, HFS: hand-foot-syndrome, NA: not available.

a Only toxicities with an incidence of 5% or more are described.

b Joined analysis.

c Of cycles.

d First 6 cycles in a row and a week of rest, followed by cycles of 2 or 3 weeks of therapy and 1 week of rest.

e Of the total study population of frail and older patient ($n = 47$).

f No candidate for combination chemotherapy because of co-morbidity or poor tolerance to prior chemotherapy (median age 74 yrs).

a persisting decrease in red cell colony forming units as well as a persisting decrease in circulating haematopoietic progenitor cells is found.[48] Pharmacokinetics of mitoxantrone seemed unaltered in the elderly[48] (Table 3).

6.2. Taxanes

Paclitaxel as well as docetaxel has mainly been studied in elderly BC patients using a weekly regimen, showing activity for both agents.[50–57] In addition there are three abstracts on the 3-weekly administration of docetaxel, showing contradictory and non-conclusive results.[58,59]

The clearance of unbound paclitaxel was significantly diminished[53,60] and the volume of distribution at a steady state was smaller in patients of $\geqslant$70 years of age[53] (Table 3). A dose of 100 mg/m^2 of paclitaxel in younger, and of 80 mg/m^2 in older patients resulted in comparable haematological pharmacodynamics, with a similar decrease in white blood cell counts.[53] Weekly administered paclitaxel (80 mg/m^2) resulted in comparable toxicity and efficacy in older and younger patients, although the younger group was significantly more heavily pre-treated (including more patients with prior taxane treatment).[50] In a pharmacokinetic study in patients >65 years of age with different types of malignancies (n = 102, 23 patients with breast cancer), treated with 3-weekly paclitaxel, a decreased clearance and increased total exposure with age was found (Table 3), resulting in a significantly lower nadir of the absolute neutrophil count (ANC) in older patients. However, the correlation between the AUC and nadir ANC was not statistically different. There was no difference in adverse events between the age groups.[61]

Ten Tije et al., observed that fatigue was the main reason to discontinue treatment with weekly paclitaxel given as first line chemotherapy for 32% of the patients.[51] The use of Geriatric Scales (Charlson score, and instrumental activities of daily life-scale) was not helpful in predicting activity or toxicity in an Italian study.[52] However, the reported clinical benefit in elderly BC patients on 'weekly' paclitaxel regimens ranges from 58% to 83%.[50–54]

In contrast to the paclitaxel clearance, the clearance of docetaxel seemed to be unaltered in the elderly,[38,62,63] although patients aged $\geqslant$65 years appeared to be more sensitive to docetaxel induced neutropaenia.[62] The latter was correlated with drug exposure and not with age.[62] Unfortunately, this study (n = 20, including 3 patients with MBC) only reported on the toxicity of the first therapy cycle.[62] A more recent pharmacokinetic study (n = 20, 10 patients with MBC) administering 35 mg/m^2 docetaxel on a weekly basis, confirmed the absence of an effect of age on the pharmacokinetics of docetaxel. However, the authors advocated to initially start with an (untested) weekly dose of 26 mg/m^2 of docetaxel based on $\geqslant$grade 3 haematological toxicity in 19% and $\geqslant$grade 3 non-haematological toxicity in 53% of the patients. Correlation of pharmacokinetic variables with geriatric assessment variables showed that a lower Lawtonscore (meaning more dependent in instrumental activities) and higher score on Geriatric Depression scale correlated with longer terminal $T_{1/2}$[63] (Table 3).

As with paclitaxel, the most important side-effect of docetaxel in the elderly was fatigue/asthenia. With respect to activity, docetaxel, administered in a weekly schedule, provided clinical benefit in 48–72% of the elderly with MBC.[38,62,64] Based on the pharmacokinetic data, a 3-weekly regimen of docetaxel 75 mg/m^2 theoretically seems feasible but data from a well designed, prospective study in a homogeneous cohort of older patients with MBC are not available.

Moreover, although no specific data exist for the elderly with elevated hepatic enzymes, dose adjustment of taxanes is recommended as in their younger counterparts.[65,66]

6.3. Vinca-alkaloids

Vinorelbine, as the only member of this family of inhibitors of microtubule polymerisation, has been tested in elderly with MBC. Most data are pointing towards unaltered pharmacokinetics in elderly,[67–69] although one group found a reduced vinorelbine clearance[70] (Table 3). A correlation between the AUC and clearance of vinorelbin and neutropaenia has been detected.[68,70] In this patient group, neutropaenia, and constipation, were found to be the most important toxicities.[68,69,72] Objective responses were seen in 30–38% of the patients,[68,69,72] while an additional 33–38% achieved stable disease.[69,72]

6.4. Fluoropyrimidines

Continuously intravenously administered 5-fluorouracil (5FU) has a decreased clearance in elderly,[73] but was never formally tested for activity in MBC. Age did not affect the AUC and peak-concentrations of 5-FU and its metabolites when administered as the prodrug capecitabine.[74] Importantly, the activity of dihydropyrimidine dehydrogenase, the initial enzyme in the catabolism of 5FU, is not affected by an increased age.[75]

The standard dose of capecitabine (1250 mg/m^2, bi-daily, days 1–14) was not feasible in older patients with MBC because of lethal toxicity (7% of the patients died due to grade 4 diarrhoea).[76] Bajetta et al., showed that capecitabine, given at a reduced dose of 2000 mg/m^2 per day, is well tolerated by elderly with MBC, although an increased incidence of toxicity, especially diarrhea, in women over 70 years as compared to women being 65–70 years of age (32% versus 10%, respectively) was observed. The incidence of nausea and stomatitis was inversely related to creatinine clearance.[76] With respect to activity, capecitabine yielded a 70–82% clinical benefit rate, being higher in chemotherapy-naive patients.[76]

In a very small study (n = 10), oral UFT induced diarrhea in all patients, being grades 3–4 in 40%. Twenty percent of the patients discontinued treatment after the first cycle because of gastro-intestinal toxicity.[77] Diarrhea was also the major adverse event (grade 3 in 11%) in elderly with MBC treated with doxifluridine, but age did not affect tolerability. The response rate was higher in chemotherapy-naive as compared to pretreated patients (30% versus 18%, respectively).[78] There are no data available on the pharmacokinetics of doxifluridine or UFT in the elderly patients.

Clearly, the relatively unpredictable and sometimes severe toxicity of fluoropyrimidines in the elderly remains a point of concern.

Table 3 – Pharmacokinetic data in the elderly patients treated with cytotoxic therapy

Agent	Ref.	Pharmacokinetic finding		Significance
Doxorubicin	[38]	Age (years)	Clearance (L/h)	$p = 0.88$
		<65	62	
		65–69	70	
		⩾70	64	
Epirubicin	[43]	Linear decline of clearance (L/h) with increasing age: 60 yr: 75; 70 yr: 65		NA
Idarubicin	[47]	No correlation between AUC for IDA or IDOL and age (no specified data available).		NA
	[44]	Grade ⩽ 2 neutropaenia: IDA $C^{through}$: 0.35 ng/ml		$p < 0.00001$
		Grade 3–4 neutropaenia: IDA $C^{through}$: 0.60 ng/ml		
		Grade ⩽ 2 neutropaenia: IDOL $C^{through}$: 3.91 ng/ml		$p < 0.000001$
		Grade 3–4 neutropaenia: IDOL $C^{through}$: 6.69 ng/ml		
Mitoxantrone	[48]	Total body clearance and renal clearance comparable with historic controls (21,22 L/h/m^2 and 1.00 L/h, respectively).		NA
Paclitaxel	[53]	Age (years)	Clearance unbound paclitaxel (L/h/m^2)	$p = 0.002$
		<70	247	
		⩾70	124	
		Age (years)	$T_{1/2}$ unbound paclitaxel (h)	NS
		<70	21.7	
		⩾70	18.0	
		Age (years)	Distribution vol unbound paclitaxel (L/m^2)	$p < 0.001$
		<70	2546	
		⩾70	1105	
	[60]	5% decrease in elimination for 10 year increase in age.		NA
	[61]	Age (years)	AUC (μmol/L*h)	$p = 0.01$
		55–64	22.4	
		65–74	26.2	
		⩾70	31.7	
		Age (years)	Total body clearance (L/h/m^2)	$p = 0.07$
		55–64	11	
		65–74	9.3	
		⩾70	8.2	
Docetaxel	[38]	Age (years)	Clearance (L/h)	$p = 0.45$
		<65	41.	
		65–69	45	
		⩾70	43.3	
	[62]	Age (years)	Clearance (L/h)	$p = 0.98$
		<65	30.0	
		⩾65	30.1	
		Age (years)	AUC (μg/mL*h)	$p = 0.86$
		<65	5.69	
		⩾65	6.01	
	[63]	Clearance 18.3 L/h, no correlation with increasing age. Lower Lawtonscore (meaning more dependent in instrumental activities) and higher score on Geriatric Depression Scale correlated with longer terminal $T_{1/2}$.		
Vinorelbine	[68]	Clearance 33.1 L/h without correlation with age.		$p = 0.11$
		Correlation between clearance and fractional survival of neutrophils ($r = 0.49$).		$p < 0.01$
	[70]	Population pharmacokinetic model: no influence of age in a covariate analysis.		NA
	[71]	Decrease in clearance with age ($r = 0.76$).		$p = 0.0068$
		Correlation between AUC and neutropaenia ($r = 0.66$).		$p = 0.0256$
Continous 5-FU	[73]	Correlation between age and clearance ($R^2 = 0.14$).		$p < 0.001$
Capecitabine	[74]	No correlation between age and AUC of 5-FU or AUC of 5′-DFUR (R^2: 0.081 and 0.047, respectively).		NS
CMF	[82]	Modest increase in clearance of 5-FU as a function of age. No effect of age on pharmacokinetics of methotrexate. No effect of age on pharmacokinetics of cyclophosphamide.		NA

Table 3 – *continued*

Agent	Ref.	Pharmacokinetic finding		Significance
AC	[28]	Age (years)	Clearance of doxorubicin (L/min/m^2)	$p = 0.88$
		<65	0.54	
		⩾65	0.47	
		Age (years)	Clearance of cyclophosphamide (L/min/m^2)	$p = 0.92$
		<65	0.04	
		⩾65	0.04	

Ref: reference, NA: not available, NS: not significant, R^2: coefficients of determination, *r*: correlation coefficient, 5-FU: 5-fluorouracil, 5′-DFUR: 5′-deoxy-5-fluorouridine, CMF: cyclophosphamide, methotrexate and 5-FU, AC: doxorubicin and cyclophosphamide, IDA: idarubicin, IDOL: idarubicinol, AUC: area under the curve, $C^{through}$: mean concentration during chemotherapy cycle, $T_{1/2}$: elimination half life.

7. Combination regimens (Table 4)

Some accepted standard combination regimens for MBC have specifically been studied in the elderly patients, as described in Table 4. Unfortunately, most of the studies have major limitations (small sample size, retrospective subset-analysis, poor study design), while data on the use of standard first-line anthracyclin-based regimens in the elderly patients are hardly available. In a retrospective analysis from 5 trials studying multidrug regimens for MBC (six different regimens, varying treatment duration), 70 women ⩾70 years were compared to randomly selected patients of <50 and 50–69 years of age, respectively. Although the performance score in the elderly cohort was worse, there was no significant difference in dose-density, toxicities or activity between the different age groups. However, a true comparison is hampered because in 3 of the 5 protocols the initial dose was reduced by 25% for patients ⩾65 years of age.[79]

7.1. *Cyclophosphamide, methotrexate and 5-fluorouracil (CMF)*

As early as 1984, a modified schedule of CMF for the elderly (⩾65 years of age) was proposed whereby the absolute dose of cyclophosphamide and methotrexate, respectively, were calculated on the basis of the creatinine clearance. Using this modification, there was no correlation of toxicity or cycle-by-cycle blood counts with age or creatinine clearance, while a significantly lower incidence of nausea and vomiting was observed at increasing age.[33] Age did not affect the response rate in elderly (modified CMF) as compared to younger patients (standard dose CMF), although overall survival was worse in the group older than 80 years.[33,77] In a rather poorly designed small non-randomised study with CMF, toxicity and response were suggested to be independent of age.[81]

In a pharmacokinetic study using CMF, no clear effect of an increasing age on the pharmacokinetics of any of the components of CMF could be found.[82] A small increase in MTX clearance was seen with an increased glomerular filtration rate.[82]

7.2. *Anthracycline/anthracendione based*

In a large retrospective subset analysis from 18 studies ($n = 1011$, 244 patients ⩾65 years; treatment period 1973–1984), doxorubicin-based combination chemotherapy was suggested to yield lower response rates in the elderly, although time to progression as well as overall survival was similar in patients ⩾65 years and patients being 50–64 years of age. The haematological toxicity caused by chemotherapy was comparable in both groups, but the dose intensity in elderly was lower (91% versus 80%).[83] Data on the cardiotoxicity of doxorubicin-based regimens in this cohort were inconsistent, whereby some studies did not find a relation between increased age and cardiotoxicity, while others did.[28,84,85]

Pharmacokinetic analysis in patients treated with adjuvant doxorubicin in combination with cyclophosphamide showed no age-related changes in clearance or distribution of either doxorubicin or cyclophosphamide.[28]

In a dose-finding study on the combination of idarubicin and cyclophosphamide in patients ⩾65 years, the dose limiting toxicities were grade 4 neutropaenia, and consequently neutropenic fever.[86] Using a different regimen, but with a dose-intensity comparable to the maximum tolerated dose of the former study, 39 patients were treated for 175 cycles, resulting in less neutropaenia (grades 3–4 neutropaenia in 3% of the cycles).[87] A large proportion of the patients (43–69%) did benefit from this treatment.[86,87]

The toxicity of the FEC combination (5FU, 4-epidoxorubicin and cyclophosphamide), reported as part of a greater retrospective analysis in patients with several types of advanced cancer, was not different in patients being younger versus older than 70 years of age. Further, the efficacy in patients with breast cancer ($n = 20$) was also similar in both age groups.[88] In a phase II study, the combination of mitoxantrone, levo-leucovorin and 5FU appeared to be active in elderly patients, without causing major toxicity.[89]

7.3. *Other combinations*

The combination of vinorelbine and capecitabine was studied in a dose finding study in patients ⩾65 years stratifying for the presence or absence of bone metastasis. More haematological toxicity was found in patients with bone involvement. The recommended dose-level in patients ⩾65 years with bone metastases was lower than for patients without bony disease (bi-daily capecitabine 1000 mg/m^2, instead of 1250 mg/m^2).[90]

Using vinorelbine in combination with gemcitabine, in a strongly selected population (26% excluded based on frailty) of women ⩾65 years of age, resulted in grades 3–4 haematological and gastrointestinal toxicity, as is shown in Table 4. Clinical benefit was observed in 74% of the patients, and

Table 4 – Studies on combination regimens of cytotoxic therapy in elderly women with metastatic breast cancer

Cytotoxic agents	Ref.	Dosage (mg/m^2)	Interval	N	Age (years)	Previous cytotoxic therapy	Neutropaenia grades 3–4	Other grades 3–4 toxicity[a]	Toxic death	PR or CR	SD
Cyclophosphamide Methotrexate Fluorouracil	[33]	[b] [b] 600	d 1–14 d 1,8 d 1,8 q 28d	92	⩾65	None	NA	All grades: N/V 58% Mucositis 18% Diarrhea 10% Infection 10%	3	42%	NA
	[80]	[b] [b] 600	d 1–14 d 1,8 d 1,8 q 28d	86	⩾65	None	NA (6 had neutrophils < 0.1)	NA (10% withdrew early from treatment due to toxicity)	1	38%	45%
	[81]	100 40 600	d 1–14 d 1,8 d 1,8 q 28d	10	>70	NA	60%	Infection 20% Mucositis 20% N/V 20% Thromboembolic 20% Thrombocytopaenia 10%	None	40%	13%[c]
	[81]	75 30 450	d 1–14 d 1,8 d 1,8 q 28d	13	>70	NA	38%	Thrombocytopaenia 23% Thromboembolic 15% Infection 7%	1	5/13	See above
Idarubicin Cyclophosphamide	[86]	10–14 200	d 1–3 d 1–3 q 21d	19	65–79	65%	47%	N/V 26% Infection 26%	None	19%	14%
	[87]	35 200	d 1 d 3–6 q 28d	39	⩾65	36%	3% (leukopaenia; of 175 cycles)	–	None	37%	31%
5-FU 4-Epidoxorubicin Cyclophosphamide	[88]	600 75 600	d 1,8 d 1 d 1 q 28d	20	>70	None	NA	NA	None	60%	NA
Mitoxantrone 5-FU Levo-leucovorin	[89]	10 500 250	d 1 d 15-16 d 15–16 q 28d	24	⩾65	50%	0% leukopaenia	–	None	50%	38%
Capecitabine	[90]	800–1000	d 1–14 Twice daily	15	⩾65	53%	40%	–	None	53%	13%

Vinorelbine		20	d 1,8 q 21d								
	[90]	800–1250	d 1–14 Twice daily	21	⩾65	43%	19%	Stomatitis 5% Diarrhea 5%	None	38%	38%
		20	d 1,8 q 21d								
Gemcitabine Vinorelbine	[91]	1000 25	d 1,8 d 1,8 q 21d	34	>65 & non-frail	54%	21%	N/V 26% Anaemia 18% Constipation 15% Thrombocytopaenia 12%	None	53%	21%
	[92]	1000 25	d 1,8 d 1,8 q 21d	12	⩾70	25%	25%	Constipation 17% Anaemia 8% Abdominal pain 8%	None	11%	67%

Ref: reference, NA: not available, q: every, d: days, PR: partial response, CR: complete respons, SD: stable disease, N/V: nausea/vomiting.
a Only toxicities with an incidence of 5% or more are described.
b Based on creatinine clearance.
c Data grouped.

improvement in quality of life was suggested, although data on the latter were only available for 56% of the patients.[91] Another trial using the combination of vinorelbine and gemcitabine in patients ⩾70 years of age was prematurely interrupted because of a low response rate and serious toxicity in 25% of the patients.[92]

8. Randomised trials (Table 5)

Only two randomised trials with adequate sample size have been published as full papers (Table 5). In a phase II study, patients aged ⩾55 years were randomised in a 2:1 ratio between capecitabine and intravenous CMF. Although not only truly 'elderly' were eligible; the mean age was 69 years and 70 years, for the capecitabine and CMF groups, respectively. The study was prematurely closed because the clinical benefit rate was significantly higher in the capecitabine group. Grades 3–4 nonhaematological toxicity of capecitabine mainly consisted of hand-foot syndrome, gastro-intestinal symptoms and fatigue, whereas CMF primarily induced gastro-intestinal toxicity.[93]

The only randomised phase III study performed in elderly with MBC compared gemcitabine to epirubicin, both administered as single agent and in a weekly regimen. Thrombocytopaenia and neutropaenia were more frequently observed in the gemcitabine group. In the patients treated with epirubicin, a decline in left ventricular ejection fraction of ⩾10% was observed in 27%, while clinically relevant cardiac events were seen in 24% of the total epirucibin group (in contrast to 17% in the gemcitabine group). Serious adverse events leading to the therapy discontinuation occurred in both groups, being 8.5% versus 6.1% ($p = 0.44$), for epirubicin and gemcitabine, respectively. Of the 28 deaths, three were considered related to treatment, all three occurring in the gemcitabine group and in patients ⩾70 years of age. With increasing age, shifts in toxicities were seen towards more frequent leukopaenia (but not neutropaenia), mucositis (in the epirubicin arm) and pulmonary toxicity (in the gemcitabine arm). Epirubicin was significantly superior to gemcitabine with respect to response rate (40.3% and 16.4%), time-to-progression (6.1 months and 3.4 months) as well as overall survival (19.1 months and 11.8 months).[94]

9. Biologicals

The administration of biologicals (molecular targeted agents) such as trastuzumab or bevacizumab have not yet been studied in the elderly with MBC. In a retrospective analysis, collecting data from 19 phase I/II studies on molecular targeted agents (total group 401 patients, of whom130 patients older than 65 years of age), toxicity was not related to age. Elderly received the same dose intensity as their younger counterparts, and the frequency and intensity of (severe) adverse events were the same.[95]

10. Considerations

The goals of treatment of elderly with MBC are the same as in younger patients, namely to palliate disease symptoms with

Table 5 – Randomised studies on cytotoxic therapy in elderly women with metastatic breast cancer

Cytotoxic agent	Ref.	Dosage (mg/m^2)	Interval	N	Age (years)	Previous cytotoxic therapy	Neutropaenia grades 3–4 (%)	Other grades 3–4 toxicity[a]	Toxic death	PR or CR	SD
Capecitabine	[93]	1255	bidaily, d 1–14 q 21d	61	⩾55	Adjuvant 25% Metastatic 0%	8	HFS 15% N/V 12% Diarrhea 8% Stomatitis 8% Fatigue 5%	3 (of 5 deaths)	30%	51%
Cyclophosphamide Methotrexate Fluorouracil		600 40 600	d 1 d 1 d 1 q 21d	32	⩾55	Adjuvant 24% Metastatic 0%	41	N/V 9%	None (of 2 deaths)	16%	44%
Gemcitabine	[94]	1200	d 1,8,15 q 28d	198	⩾60	Adjuvant 20% Metastatic 0%	25	Thrombocyto-paenia 9% N/V 7% ASAT/ALAT 6% Anaemia 5%	3 (of 17 deaths)	16%	43%
Epirubicin		35	d 1,8,15 q 28d	199	⩾60	Adjuvant 19% Metastatic 1%	18	N/V 7% Anaemia 6%	None (of 11 deaths)	40%	35%

Ref: reference, PR: partial response, CR: complete respons, SD: stable disease, N/V: nausea/vomiting, HFS: hand-foot-syndrome.
a Only toxicities with an incidence of 5% or more are described.

preservation of quality of life as much as possible, and to prolong time to progression as well as overall survival. The reluctance of the oncologist to treat elderly with chemotherapy is mainly based on the subjective appreciation of the condition of the patient, while this reluctance is not shared by the patients. Co-morbidity and drug–drug interactions due to polypharmacy are encountered more frequently in the elderly and pose a serious problem in the management of this group. The interesting pilot study by Extermann et al., evaluating a predictive risk index will hopefully be further developed, providing a useful predictive scoring system.

As has been reviewed, data indicate that single agent chemotherapy as well as multi-agent regimens are tolerable and effective in the elderly. Based on the forementioned data and in view of the limitations of the reported studies, however, no specific regimen can be recommended as optimal standard. Proposals for algorithms for the cytotoxic treatment of the elderly with MBC are, because of lacking data, mostly non-evidence based.[7,96,97] The current most accepted therapies for younger patients (anthracylin-based regimens and taxanes) also appear to be reasonable options for the elderly with MBC, but it should be kept in mind that nearly all data were obtained from relatively healthy older patients, and concerning taxanes from weekly regimens. The ease of an oral regimen, as is the case for capecitabine, may be attractive for the elderly cohort.

One of the major drawbacks of cytotoxic therapy in the elderly is neutropaenia. EORTC guidelines based on a methodological review of data regarding the use of colony-stimulating factors in the elderly cancer patients, concluded that there is no evidence for the use of colony-stimulating factors in patients with MBC.[98] This guideline as well as the more recent guideline concerning the use of granulocyte-stimulating factor in adult patients does acknowledge advanced age as a risk factor for the occurrence of neutropenic fever. Both guidelines do not preclude the use of colony-stimulating factors in high-risk patients.[98,99] Whether this translates in an improved survival in MBC remains to be studied.

Pharmacokinetic comparisons between younger and older people will provide important information and be of great help. For example, based on the knowledge that paclitaxel clearance is decreased in elderly, a trial was conducted to show the pharmacodynamic equivalence of standard dose paclitaxel in younger patients and a lower dose in the elderly.[53] Procuring more pharmacokinetic data will definitely help determining the most optimal treatment regimen for the elderly with MBC.

11. Conclusion

The willingness of elderly MBC-patients to receive chemotherapy is very high. Unfortunately, the available literature data are scarce and have major limitations, hampering the reversal of the reluctance of oncologists to administer chemotherapy in older patients. Currently, there are no additional instruments yet, apart from those used in the general BC population, that are predictive for efficacy or toxicity in the elderly. In general, elderly have a higher risk to become neutropaenic due to cytotoxic therapy. Further, some chemotherapy regimens result in comparable toxicities, while other regimens have an altered toxicity-pattern in the elderly with MBC as compared to their younger counterparts.

Differences between older and younger patients generated by pharmacokinetic analysis during treatment with a specific cytotoxic regimen, could be used to convert the commonly used regimen in the younger patients to a pharmacodynamic equivalent for the elderly. If pharmacokinetic analysis does not show a difference between younger and older patients, the only useful goal of exploring a different dosing strategy is to obtain a lower incidence of neutropaenia.

Based on the current diversity and paucity of data it is difficult to recommend a specific regimen as an optimal standard for the elderly with MBC, although an approach different from the one in younger patients does not yet seem justified. To increase our knowledge and evidence-based data, further studies should be activated for the elderly cohort, and treatment within a study-protocol seems the most appropriate.

Conflict of interest statement

None of the authors has a conflict of interest.

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