Part 2

Methodological aspects of research in older breast cancer patients

Chapter 7

Choosing relevant endpoints for older breast cancer patients in clinical trials

An overview of all current clinical trails on breast cancer treatment

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Abstract

Background

With the ongoing ageing of western societies, the proportion of older breast cancer patients will increase. For several years, clinicians and researchers in geriatric oncology have urged for new clinical trials that address patient-related endpoints such as functional decline after treatment of older patients. The aim of this study was to present an overview of trial characteristics and endpoints of all currently running clinical trials in breast cancer, particularly in older patients.

Methods

The clinical trial register of the United States National Institutes of Health Differences was searched for all current clinical trials on breast cancer treatment. Trial characteristics and endpoints were retrieved from the register and differences in characteristics between studies in older patients specifically (defined as a lower age-limit of 60 years or older) and trials in all patients were assessed using Chi-square tests.

Results

We included 463 clinical trials. Nine trials (2%) specifically investigated breast cancer treatment in older patients. Ninety-one breast cancer trials included any patient-related endpoint (20%), while five trials specifically addressing older patients included any patient-related endpoint (56%, P=0.02). Five of the trials in older patients incorporated a geriatric assessment (56%).

Conclusion

Clinical trials still rarely incorporate patient-related endpoints, even in trials that specifically address older patients. Trials that are specifically designed for older patients do not often incorporate a geriatric assessment in their design. This implicates that current clinical studies are not expected to fill the gap in knowledge concerning treatment of older breast cancer patients in the next decade.

Introduction

Breast cancer is the leading contributor to cancer incidence and mortality in women worldwide[1]. With the on-going ageing of western societies, the proportion of older breast cancer patients will increase. Older patients comprise a heterogeneous group due to differences in comorbidity, functional status, physiological reserves and geriatric syndromes[2;3]. These characteristics of older patients importantly affect both effectiveness as well as side effects of treatment strategies.

A recent position paper of the International Society for Geriatric Oncology (SIOG) stated that patient-related endpoints such as functional status, cognitive function and quality of life are considered equally or even more important than standard endpoints such as survival and recurrence, in order to balance benefits and risks of cancer therapy in older patients[4]. The SIOG as well as many researchers and clinicians in the geriatric oncology field have been urging for new studies in older cancer patients that address endpoints such as functional decline and quality of life after treatment [4-9]. Until now, clinical trials often only addressed endpoints such as overall survival and recurrence.

As it takes many years from conception of a study until the publication of its final results, any progress in the next ten years is most likely to come from studies that are currently ongoing. However, this will only add to current knowledge if these studies address the endpoints that are relevant for older patients and not exclusively include healthy older patients. Therefore, the aim of this study was to present an overview of characteristics and endpoints of all current clinical trials in breast cancer, with a special focus on older patients.

Methods

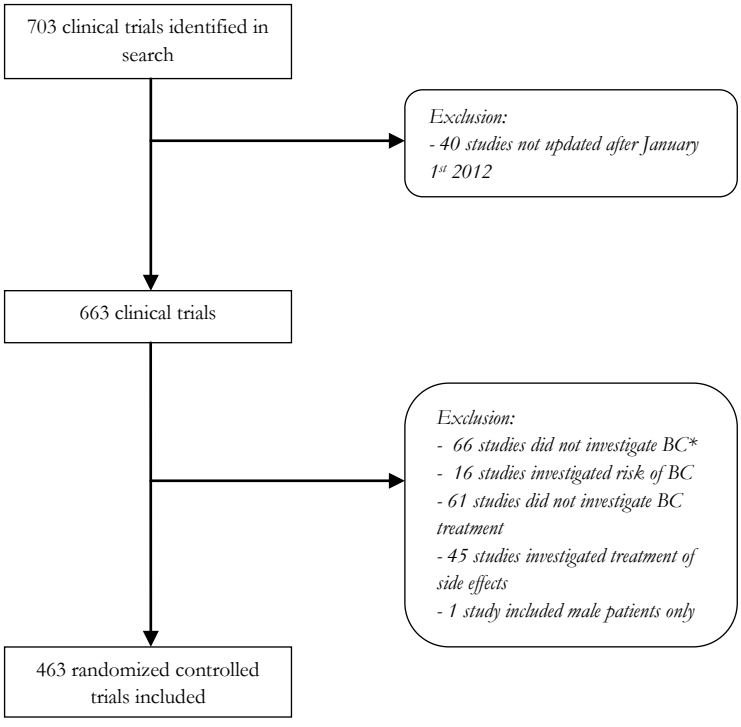
The clinical trial register of the United States National Institutes of Health (www.clinicaltrials.gov) was searched on November 10th 2013 using the search term “breast cancer”. We included all Phase II, III and IV clinical trials that investigated endpoints of breast cancer treatment and that were currently recruiting patients or were planning to start recruiting. Phase IV studies were only included if they were randomized. Phase I trials were not included, as the endpoints of these trials are by definition not patient-related.

Studies with unknown recruitment status as well as studies that were not updated after January 1st 2012 were excluded. Furthermore, studies that investigated reconstructive surgery or

treatment of the side-effects of breast cancer therapy such as musculoskeletal symptoms after endocrine treatment, as well as diagnostic studies were not included.

For all included studies, we extracted the following data from the trial registry: study phase, type of treatment(s) evaluated (chemotherapy, endocrine therapy, biologicals, radiotherapy, surgery or "other"), and funding (industry or "other"). We registered the following inclusion criteria of all selected studies: disease stage (metastasized, non-metastasized or both), hormone receptor status, her2-expression, age limits and performance status according to the Karnofsky index as well as the World Health Organization (WHO) performance status. If studies used Karnofsky performance status only, we calculated WHO performance status in line with previous studies10 based on the Karnofsky performance status as follows: Karnofsky performance status 100% = WHO performance status 0; Karnofsky performance status 80-99% = WHO performance status 1; Karnofsky performance status 60-79 = WHO performance status 2, Karnofsky performance status 40-69 = WHO performance status 3 and Karnofsky performance status below 40 = WHO performance status 4.

Figure 1 *Flow diagram of included studies from the clinical trial register*



Both primary and secondary endpoints of included studies were registered and categorized into eleven categories (Suppl. Table 1): overall survival, disease-free survival, response, toxicity, compliance, pharmacological parameters, biological outcome parameters, health care utilization, quality of life, functional status and cognitive functioning. Overall survival, disease-free survival, response, toxicity, compliance, pharmacological parameters, biological outcome parameters and health care utilization were defined as standard endpoints. Quality of life, functional status, cognitive functioning and cosmetic outcome were defined as patient-related endpoints. A study solely in older patients was defined as a lower age-limit of 60 years or older.

Statistical analyses

All analyses were performed in IBM SPSS Statistics version 20.0. A p-value smaller than 0.05 was considered as statistically significant.

Endpoints of studies solely in older patients were compared with endpoints of studies in all patients using Chi-square tests. Similarly, differences in study characteristics between studies that incorporated patient-related endpoints and studies that did not were assessed using Chi-square tests.

Results

Overall, 703 clinical trials were identified in the Clinical Trial Register, of which 463 studies were included (Figure 1).

Study characteristics of included trials are presented in Table 1. Nine studies (2%) investigate breast cancer treatment in older patients (lower age limit >=60 years of age) specifically. Most trials do not have an upper age limit (82%), but the majority of trials do exclude patients based on WHO performance status (40% excluded WHO performance status of 2 or higher and 37% WHO performance status of 1 or higher). Most trials are Phase II (60%) or Phase III (23%) trials and investigated chemotherapy (42%) or biologicals (52%).

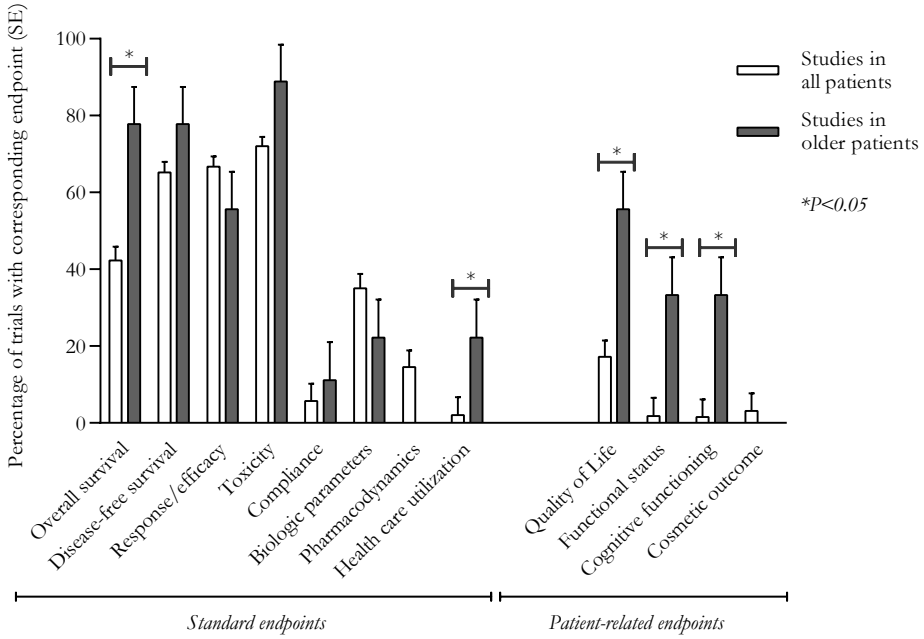
All endpoints of studies in all patients as well as studies in older patients specifically are depicted in Figure 2. Frequent standard endpoints are overall survival (42% in studies in all patients versus 78% in studies in older patients specifically, P=0.04), disease-free survival (65% studies in all patients versus 78% in studies in older patients specifically, P=0.35) and response (67% of studies in all patients versus 56% of studies in older patients specifically, P=0.35). Studies in older patients more frequently incorporate patient-related endpoints including quality

Table 1 *Characteristics of included trials*

	All trials (N=463)	
	N	(%)
Study in older patients only[a]		
Yes	9	(2)
No	454	(98)
Upper age limit		
None	381	(82)
0-50	2	(0.5)
51-64	1	(0.5)
65-69	6	(1)
70-74	32	(7)
75-79	24	(5)
≥ 80	17	(4)
Performance status included		
All	101	(22)
0	2	(0)
0 to 1	169	(36)
0 to 2	183	(40)
0 to 3	8	(2)
Stage		
Non metastasized only (0-III)	194	(42)
Metastasized only (IV)	153	(33)
Both non metastasized and metastasized	116	(25)
Hormone receptor status		
Positive	90	(19)
Negative	56	(12)
Both	317	(69)
Her2 Neu receptor status		
Positive	80	(17)
Negative	146	(32)
Both	237	(51)
Phase		
I & II	63	(13)
II	277	(60)
II & III	12	(3)
III	106	(23)
IV	5	(1)
Industry sponsored		
Yes	179	(39)
No	284	(61)
Intervention[b]		
Chemotherapy	193	(42)
Endocrine therapy	65	(14)
Biologicals	242	(52)
Radiotherapy	47	(10)
Surgery	17	(4)
Other	46	(10)

[a]Include patients aged 60 years and older only; [b]Studies can investigate more than one intervention

Figure 2 *Endpoints of studies in older patients compared to studies in all patients*



of life (56% of studies in older patients specifically versus 17% of studies in all patients, P=0.01), functional status (33% of studies in older patients specifically versus 2% of studies in all patients, P=0.001) and cognition (33% of studies in older patients specifically versus 2% of studies in all patients, P=0.005).

Table 2 shows the characteristics of studies that incorporate patient-related endpoints as either a primary or secondary endpoints, compared to studies that do not. Again, these analyses show that studies in older patients more frequently incorporate any patient-related endpoint (56% in studies in older patients specifically versus 20% in studies in all patients, P=0.02). Studies that investigate the use of biologicals are less likely to incorporate patient-related endpoints compared to other studies (15% of all studies that investigate biologicals compared to 27% of other studies, P=0.002), while studies in radiotherapy and surgery incorporate patient-related endpoints more frequently than other studies (53% of studies that investigate radiotherapy compared to 17% of other studies, P<0.001 and 47% of studies that investigate surgery compared to 20% of other studies, P=0.006 respectively).

Table 3 shows characteristics and endpoints of the nine studies solely targeting older patients. Five studies (56%) include some kind of a geriatric assessment as baseline measurement. The majority of studies exclude patients based on WHO performance status . In two studies (22%),

Table 2 *Characteristics of trails in relation to patient-related endpoints*

	Patient-related endpoint[a]		**No patient-related endpoint**		
	n/N	(%)	*n/N*	(%)	*P-value*
Study in older patients only[b]					
No	91/454	(20)	363/454	(80)	*0.02*
Yes	5/9	(56)	4/9	(44)	
Stage					
Non metastasized only (0-III)	46/194	(24)	148/194	(76)	*0.37*
Metastasized only (IV)	27/153	(18)	126/153	(82)	
Both non metastasized and metastasized	23/116	(20)	93/116	(80)	
Industry sponsored					
No	60/284	(21)	224/284	(79)	*0.79*
Yes	36/179	(20)	143/179	(80)	
Intervention					
Chemotherapy					
Yes	33/193	(17)	160/193	(83)	*0.10*
No	63/270	(23)	207/270	(77)	
Endocrine therapy					
Yes	16/65	(25)	49/65	(75)	*0.41*
No	80/398	(20)	318/398	(80)	
Biologicals					
Yes	37/242	(15)	205/242	(85)	*0.002*
No	59/221	(27)	162/221	(73)	
Radiotherapy					
Yes	25/47	(53)	22/47	(47)	*<0.001*
No	71/416	(17)	345/416	(83)	
Surgery					
Yes	8/17	(47)	9/17	(53)	*0.006*
No	88/446	(20)	358/446	(80)	
Other					
Yes	10/46	(22)	36/46	(78)	*0.86*
No	86/417	(21)	331/417	(79)	

[a]Patient-related endpoint is defined as at least one of the following endpoints: quality of life, functional status, cognitive status or cosmetic outcome; [b]Included patients aged 60 years and older only

only patients with a performance status of 0 or 1 are included. In five studies (56%), only patients with a performance status of 0 to 2 are included and in one study only patients a with performance status of 0 to 3 are included). Five out of nine studies (56%) are performed in patients with early stage breast cancer and investigate chemotherapy or biologicals. Three out of nine studies (33%) incorporate functional status or cognitive status as study endpoint.

Discussion

This study shows that only 2% of all ongoing clinical trials on breast cancer treatment are specifically designed for older patients. A small minority of trials incorporate any patient-related endpoint. Although studies in older patients do incorporate patient-related endpoints more frequently, half of these studies focus exclusively on treatment- or disease-related endpoints.

There are endless options if it comes to the choice of endpoints for clinical trials. The majority of current clinical trials use standard endpoints such as overall survival, disease-free survival or breast cancer survival. However, the SIOG position paper of 2013 states that although these endpoints are important to assess the efficacy of treatment, patient-related endpoints are crucial to weigh risks and benefits of treatment[4]. It has been suggested that the acute or chronic toxicities caused by cancer-directed therapy can lead to decreased quality of life and functional status, particularly in the vulnerable elderly population[4]. Therefore, quality of life and preservation of functional capacity are essential endpoints to determine if patients can tolerate certain treatments. In addition, decline of functional capacity has been shown to be independently related to survival outcomes of breast cancer patients[3]. Furthermore, loss of functional capacity can make the difference between independent living and institutionalization of older patients.

In addition, cognitive function is an endpoint that is particularly of interest for trials that study adjuvant therapy, as it has been suggested that long-term treatment with adjuvant therapy may result in a decline of cognitive function[11]. Several studies have suggested that although older patients are willing to receive adjuvant therapy[12], they are less willing to trade absolute survival gain for negative impact on quality of life, functional independence and cognitive function[13-15].

Another reason why these patient-related endpoints are so important, is that older patients have an increased risk of dying of non-cancer related causes[16]. Due to these so-called competing causes of death, absolute survival benefits of therapy may be less pronounced in the older population and therefore, careful balancing of the benefits of treatment with the short- and long-term side-effects is of particular importance[4]. However, there are still no data available that enable doctors to provide their older patients with an evidence-based advice concerning these endpoints.

Concerning characteristics of different trials, it is striking that even studies that target metastasized breast cancer rarely include any patient-related endpoint measures, even

Tabel 3 *Characteristics end andpoints of studies that were performed in older patients only (age >60 years, N=9)*

	N	(%)
Trial characteristics		
Geriatric assessment at baseline		
No	4	(44)
Yes	5	(56)
Performance status *(inclusion criterium)*		
All	1	(11)
0 to 1	2	(22)
0 to 2	5	(56)
0 to 3	1	(11)
Stage *(inclusion criterium)*		
Non metastasized only (0-III)	5	(56)
Metastasized only (IV)	3	(33)
Both non metastasized and metastasized	1	(11)
Industry sponsored		
Yes	6	(67)
No	3	(33)
Intervention[a]		
Chemotherapy	5	(56)
Endocrine therapy	2	(22)
Biologicals	5	(56)
Radiotherapy	1	(11)
Surgery	1	(11)
Other	0	(0)
Endpoints		
Quality of life		
Not included	4	(44)
Included	5	(56)
Functional status		
Not included	6	(67)
Questionnaire (ADL/IADL)	1	(11)
Included but not specified	2	(22)
Cognitive status		
Not included	6	(67)
MMSE	1	(11)
Included but not specified	2	(22)

[a]*Studies could investigate more than one intervention*

though one would expect that this must be the most important endpoint in a palliative treatment setting. Studies addressing surgical treatment and radiotherapy incorporate patient-related endpoints most frequently, but these are generally limited to cosmetic outcomes after

radiotherapy and pain-related endpoints after surgery. Studies that investigate chemotherapy, endocrine therapy, and biologicals incorporate patient-related endpoints in less than one-third of all studies, even though these therapies often lead to long-term toxicity and potentially to a decreased quality of life[17;18]. Especially endocrine therapy is often prescribed in the older population and often leads to long-term toxicity and nonpersistence in this population[17;19].

Interestingly, we identified very few studies that specifically target older patients, despite the fact that the need for such studies is widely acknowledged[4;5]. Also, 89% of these studies exclude patients based on their performance status, which means that a large proportion of older patients will not be able to participate in these trials, thereby limiting the generalizability of study endpoints for the actual patient population. As a result, recommendations for treatment of the general older breast cancer population will remain "expert-based". Furthermore, only half of these studies incorporate patient-related endpoints, and only five studies (56%) include a geriatric assessment, despite the fact that this is strongly recommended in order to be able to compare study populations, to adjust for baseline impairments and to predict outcomes of treatment in subgroups of older cancer patients[5;20].

Our findings are alarming, and indicate that all the efforts of the clinical community and organizations such as the International Society for Geriatric Oncology (SIOG) have not resulted in an increase in studies in older breast cancer patients, and the studies that are performed do still not incorporate relevant endpoints or a geriatric assessment. This could be explained by the fact that obtaining funding for studies in geriatric oncology can be difficult. Furthermore, studying patient-related endpoints can be time-consuming as it generally requires performing additional questionnaires and tests. In upcoming decades, the number of older breast cancer patients in developed countries will rise due to the ageing of Western societies. Hence, the number of patients that we cannot provide with an evidence-based treatment recommendation will strongly increase if future trials do not incorporate patient-related endpoints in their trial designs.

As an alternative to randomized controlled trials in older cancer patients, observational studies could serve as a means to study treatment strategies, as they tend to be more representative for the older breast cancer population[4;21;22]. Provided that adequate methodological methods are used and the relevant endpoints are addressed, observational studies could be a reasonable alternative to fill the gap of knowledge in geriatric oncology in the future[4]. Furthermore, assessing specific endpoints such as adverse events, cognitive and functional decline may be more feasible in prospective observational studies, as these studies are generally more easy to perform than clinical trials.

Strengths and limitations

To our knowledge, this is the first study that provides an overview of endpoints of current clinical trials on breast cancer treatment. The most important limitation of this study is the fact that we only focused on studies that were registered in the National Institutes of Health clinical trial registry. However, this is by far the largest and most commonly used registry in the world. Second, we relied on the data recorded in the clinical trial registry. It is possible that additional endpoints were present in study protocol but not included on the website. However, it is unlikely that this occurs on a large scale.

Conclusion

A recent position paper of the International Society of Geriatric Oncology stated that patient-related endpoints such as quality of life and preservation of functional capacity and independence are important for older cancer patients, and should be included more often as endpoints in clinical trials in this population[4]. Although this request has been made for several years[5;6;8], our data show that clinical trials still rarely incorporate these endpoints in their study design, even in studies for older patients specifically. Furthermore, even studies that are specifically developed for older patients exclude a large proportion of older patients based on their inclusion criteria. Therefore, currently ongoing clinical trials are unlikely to provide major improvements in our knowledge of the treatment of older breast cancer patients. Observational studies could be a reasonable alternative method to study treatment effects in the older breast cancer population in the future, provided that adequate methodology is used.

Suppl. Table 1 *Classification of study endpoints*

Study endpoint	Classification
Overall survival	Overall survival
Mortality	
Disease-free survival	Disease-free survival
Progression-free survival	
Event-free survival	
Time to progression	
Toxicity	Toxicity
Safety	
Adverse events	
Maximum tolerated dose	
Response	Response
Efficacy	
Time to response	
Completion of planned treatment	Compliance
Compliance to treatment	
Achieved dose intensity	
Pharmacokinetics	Pharmacological parameters
Pharmacodynamics	
Health care utilization	Health care utilization
Health economics	
Cost-effectiveness	
Laboratory parameters	Biological outcome parameters
Genetic parameters	
Tumour biology	
Quality of life	Quality of life
Pain	
Fatigue	
Care dependence	Functional status
Institutionalization	
Functional status	
Performance status	
Cognitive functioning	Cognitive functioning
Cognitive decline	

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