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SPECIAL ARTICLE

End Points and Trial Design in Geriatric Oncology Research: A Joint European Organisation for Research and Treatment of Cancer–Alliance for Clinical Trials in Oncology–International Society of Geriatric Oncology Position Article

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ABSTRACT

Selecting the most appropriate end points for clinical trials is important to assess the value of new treatment strategies. Well-established end points for clinical research exist in oncology but may not be as relevant to the older cancer population because of competing risks of death and potentially increased impact of therapy on global functioning and quality of life. This article discusses specific clinical end points and their advantages and disadvantages for older individuals.

Randomized or single-arm phase II trials can provide insight into the range of efficacy and toxicity in older populations but ideally need to be confirmed in phase III trials, which are unfortunately often hindered by the severe heterogeneity of the older cancer population, difficulties with selection bias depending on inclusion criteria, physician perception, and barriers in willingness to participate. All clinical trials in oncology should be without an upper age limit to allow entry of eligible older adults. In settings where so-called standard therapy is not feasible, specific trials for older patients with cancer might be required, integrating meaningful measures of outcome. Not all questions can be answered in randomized clinical trials, and large observational cohort studies or registries within the community setting should be established (preferably in parallel to randomized trials) so that treatment patterns across different settings can be compared with impact on outcome. Obligatory integration of a comparable form of geriatric assessment is recommended in future studies, and regulatory organizations such as the European Medicines Agency and US Food and Drug Administration should require adequate collection of data on efficacy and toxicity of new drugs in fit and frail elderly subpopulations.

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INTRODUCTION

The choice of appropriate end points is important to assess the benefit of therapy. In oncology, there are well-established clinical end points for clinical research in randomized clinical trials (RCTs); in the curative/adjuvant setting, disease-free survival (DFS) and overall survival (OS) are the most recognized and well accepted. For metastatic solid tumors, progression-free survival (PFS), time to tumor progression (TTP), time to treatment failure (TTF), response rate (RR), and OS are the most commonly used end points.

A caveat is that the definitions of these so-called standard outcomes have varied in different trials in the past, challenging the ability to compare across studies and provide evidence-based care. There are international efforts to streamline this, such as the DATECAN (Definition for the Assessment of Time-to-Event End Points in Cancer Trials) project.[1]

However, these standard end points may not be the most appropriate to balance the benefits with the risks of therapy in older patients with cancer, because older patients often die as a result of other diseases, and relapse will not always affect survival, whereas cancer-directed therapy can sometimes cause severe acute or chronic toxicities and decreased quality of life (QoL). For young patients with familial/social obligations (eg, toward young children), prolongation of life might be the most important end point; however, older adult patients with incurable disease may prefer QoL above quantity of life, especially if treatment also has an impact on their functional capacity and ability to carry out

daily tasks, their cognitive function, their social situation/capability to stay at home, or their caregiving abilities.[2] Therefore, there is a need for delineation of relevant clinical end points for older individuals, which can then be uniformly incorporated into future clinical trials.[3,4]

The best-established form of clinical trial design is the RCT. When designing RCTs for older patients with cancer, selection of what should be the standard arm may vary because this can be different for fit, vulnerable, and frail patients. As a result, it will often not be possible to have the same standard arm for all older patients, so other trial designs should be considered, especially for vulnerable and frail patients.

This article describes several potential outcome measures/end points and their advantages and disadvantages for elderly-specific clinical trials and discusses potential trial designs that could be used to greatly expand evidence-based treatment outcomes for the older population with cancer.

OUTCOME MEASURES/END POINTS FOR CLINICAL TRIALS IN OLDER INDIVIDUALS

OS

OS is considered the gold standard in clinical trials, especially when evaluating the superiority of new treatments; other end points such as PFS and DFS are commonly used to report on clinical benefit, but this has been subject to criticism (Table 1).[5] Surrogacy of these end points for OS has been demonstrated in some specific settings and is under investigation in others. Compared with younger patients, elderly patients with cancer often present with significant comorbidities and therefore die as a result of other, non–cancer-related diseases more frequently.[6,7] Elderly patients are more likely to experience severe toxicities from cancer-directed therapies, including treatment-related mortality.[8,9] Non–disease-related deaths and treatment discontinuation/reduced dosage because of toxicity might dilute treatment benefit, and larger sample sizes would be needed to demonstrate treatment effects. It should be emphasized that this diluted benefit is an accurate estimate of the true clinical benefit in the older population, and larger sample sizes are the price society has to pay if it wants to ensure that older patients are not subjected to toxic therapies that provide no tangible clinical benefit. The mentioned concerns have resulted in age limits and stringent inclusion criteria, leading to the exclusion of large numbers of older patients from clinical trials.[3,10,11] Although excluding older patients with comorbidities could help a trial determine whether a benefit from treatment exists (especially if the benefit is small), this approach limits generalizability of the treatment for the vast majority of cancers, where most of the patients are older. On average, the trial population in chemotherapy trials is 5 to 10 years younger than the general population with the disease. Because there are no regulatory requirements for establishing the efficacy or toxicity of new therapies in older adults, the limited data in this population ultimately lead to the risk of expensive treatments being used in the older, less studied population, resulting in higher toxicity and smaller benefit than in younger patients with cancer.

Disease-Specific Survival

Whereas primary end points such as OS or PFS would still be suitable to provide a realistic estimation of treatment benefit in the targeted population in the presence of competing risks, measuring cancer-specific end points such as disease-specific survival (DSS) and performing competing risks analyses could generate crucial data. Nout et al[12] nicely demonstrated that including or excluding non–breast cancer–related deaths and contralateral breast cancer significantly affected outcome reporting in early breast cancer. DSS better indicates how many patients die as a result of disease and how many die as a result of other causes. A precondition to using DSS as the primary end point is that the cause of death can be reliably ascertained, and other causes of death are not related to the treatment. In that case, DSS as the primary end point might help in requiring a smaller sample size.[13] However, a reduction in the risk of one type of event (eg, death resulting from cancer) can lead to an increase in the number of observed events for competing types, just because patients remain at risk for those events for a longer period. At any rate, information on cause of death should always be reported to distinguish cancer deaths from treatment-related deaths and deaths resulting from other causes. We recommend reporting DSS always in addition to OS.

Coprimary End Points

Coprimary end points should also be considered because this allows capturing more than efficacy alone. Multiple single end points can be chosen as coprimary end points of equal importance, and a statistical design can be built to test each separately. However, coprimary end points also have disadvantages; statistical design is difficult because the correlation between the different end points is rarely known. Moreover, if the trial objective is to have positive results for at least one or all coprimary end points, the type I or II error, respectively, must be adjusted for multiple testing, which necessitates in increase of sample size.[14]

Composite End Points

Composite end points are another way of integrating other aspects into the end point, such as QoL, treatment effects on disease-related symptoms, functional capacity, and ability to carry out daily tasks. As the International Conference on Harmonisation stated,[15] composite end points avoid the need for arbitrary choice and deal with multiplicity in an efficient manner when several outcome measures are of equal importance to the patient. A composite end point in an RCT consists of multiple single end points that are combined so that an event is indicated if any of the end points occurs. Composite end points have sometimes been used in oncology (eg, skeletal-related events in clinical trials with bisphosphonates or denosumab[16]) but have been more widely used and studied in other medical disciplines, mainly in cardiology.[17,18] Major advantages of a composite end point are the simplicity of the statistical design, which is based on a single end point (ie, the composite one), and the resultant increase in statistical efficiency. However, there are also risks, and caution must be applied. The major possible issues include: lack of a strong rationale given for the composite (ie, mixture of end points with different clinical importance; eg, death and hospital admission), difficulty in interpretation of the results in case of positive results on the composite but observed divergent effects on the components, and inadequate or incorrect reporting of the results (eg, declaring positive effects on the most important component when statistical significance is only reached for the composite, and when the more important component, such as death, accounts only for a minority of the events). Less frequent but important to consider is the situation in which negative results can be observed for the composite, while

Table 1. Relevant End Points in Clinical Trials in the Older Cancer Population

End Point	Definition	Current Situation	Pro	Con
OS: time or proportion	Time from diagnosis of treatment situation/study entry until death or rate of patients alive at specified time point	Considered gold standard in clinical trials, especially when evaluating superiority of new treatments	Remains hardest end point, also in elderly	Oncologic relevance in elderly can be hampered by increased number of non–cancer-related deaths (all life ends with death)
			Easy and distinct to measure, high impact for patients	Does not include QoL aspects
DSS: time or proportion	Time from diagnosis of treatment situation/study entry until death resulting from index disease or rate of patients without death related to index disease at specified time point	Important to collect in addition to OS because it gives better insight into contribution of non–cancer-related deaths	Cancer treatment primarily aims at decreasing cancer death	Some cancer treatments might also influence non–cancer-related deaths (eg, treatment-related mortality) May lead to overestimation of true benefit for patients in presence of competing risks (eg, treatment benefit in localized prostate cancer) Reason for death will be of no/minor meaning for patients Reason for death can remain unclear
Coprimary end points	Combination of ≥ two equal primary end points	Rarely used in oncology	Allows capturing more than efficacy alone	Difficult statistical design because correlation between different end points is rarely known
				Might increase sample size
Composite end points	Combination of different end points in one defined end point	Rarely used in oncology (one example: skeletal-related events) but should be encouraged more	Can take into account multiple dimensions in definition of treatment benefit, including efficacy and toxicity	Requires individual components of composite that are clinically meaningful and of similar relative importance
			Simple and efficient statistical design Allows separate reporting of different end points	Difficult interpretation if there are divergent results for each component separately
TFFS and TTF: time or proportion	TFFS is time elapsing between random assignment and early treatment discontinuation because of any reason (including disease progression, treatment toxicity, early death), disease progression, death (resulting from any cause), or any other event of interest; TTF is similar, but death resulting from other cause is not considered an event	Often used in addition to OS	Integrates efficacy and toxicity	Difficult to distinguish between efficacy and toxicity (eg, toxic but effective) Treatments might be stopped for other reasons (eg, chemotherapy holiday)
QoL-related end points: level at specified time point or time until deterioration compared with baseline	Evaluation of QoL through validated instruments at baseline and during course of disease/treatment/study	Often used as secondary end point in clinical trials but should be promoted as primary end point or part of composite end point	QoL may be more important than duration of life for many older individuals	Difficult to measure and identify clinically relevant cutoffs that determine whether therapy is worthwhile
Maintenance of functional capacity/dependence: level at specified time point or time until deterioration compared with baseline	Evaluation of evolution of functioning and (in)dependence through validated instruments during course of disease/treatment/study	Rarely measured in oncology trials but crucial to include	Main contributor to QoL in elderly patients with cancer	No general consensus on optimal measurement or clinically relevant cutoffs determining whether therapy is worthwhile

Abbreviations: DSS, disease-specific survival; OS, overall survival; QoL, quality of life; TFFS, treatment failure–free survival; TTF, time to treatment failure.

statistical significance can be reached for the most important component. The pros and cons of composite end points have been summarized by Kleist.[19] Use of this approach is usually justified under the following assumptions:

- The individual components of the composite are clinically meaningful and of similar relative importance to clinical care.
- The expected effects on each component are similar based on clinical/biologic plausibility (which is, in the end, the rationale for using a composite end point).
- For the study to be ultimately positive, the clinically more important components of a composite end point should at least not be affected negatively.

All components of a composite end point should also be analyzed separately and reported as such. The separate reporting of end points is also essential to facilitate cross-study comparisons (although there are also intrinsic limitations to this) or to generate assumptions for designing future trials. It is important to mention that for the US Food and Drug Administration, a regulatory end point should clearly distinguish the efficacy of the drug from toxicity, patient or physician withdrawal, or patient intolerance.[20]

An interesting example of a composite end point in older individuals is therapeutic success.[21] This end point combines efficacy, toxicity, and patient compliance with treatment and has been defined as a patient receiving at least three cycles of chemotherapy, at the planned dose (without dose reduction) and schedule (no treatment delay beyond 2 weeks), and having a response (either complete or partial) without experiencing grade 3 or 4 toxicity according to the Common Toxicity Criteria criteria.[22] Variations of this design are possible, such as defining therapeutic success as being progression free at a fixed time point without having grade 3 or 4 nonhematologic or grade 4 hematologic toxicity. This seems to be an attractive end point in settings where significant differences in toxicity between two treatments are expected and requires further exploration. Looking simultaneously at toxicity and efficacy can be a disadvantage as well as an advantage; therapies might be temporarily toxic, requiring dose reduction, but might be efficacious. Dose, toxicity, and response are related (eg, in patients with non–small-cell lung cancer, those with a higher rate of hematologic toxicity survive longer[23]).

Another example is the use of overall treatment utility (OTU) as an end point in the FOCUS (Fluorouracil, Oxaliplatin, and CPT11 [irinotecan]—Use and Sequencing) trial of older patients with metastatic colorectal cancer,[24] in which good OTU indicated no clinical or radiologic evidence of disease progression and no major negative treatment effects in terms of toxicity or patient acceptability. Intermediate OTU signified either clinical deterioration but no negative treatment effect or a significant negative treatment effect but no clinical deterioration. Poor OTU indicated both clinical deterioration and a major negative treatment effect or death.

Treatment Failure–Free Survival and TTF

Treatment failure–free survival (TFFS) and TTF are well-known examples of composite end points and could also be interesting end points to consider for clinical trials in the elderly. TFFS is defined as the time that elapses between random assignment and early treatment discontinuation because of any reason (including treatment toxicity and patient refusal of further treatment), disease progression, death resulting from any cause, or any other event of interest. TTF is similar, but only disease-specific and treatment-related deaths are considered events. Treatment-related toxicity is a major issue in elderly patients with cancer, especially those with advanced disease stages where the goal of treatment is palliation rather than cure. TFFS and TTF provide an opportunity to take into account the role of toxicity and not concentrate only on efficacy. This is important because older patients are less willing than younger patients to continue treatments with severe toxicities,[2,25] especially if these have functional consequences that limit independence. One limitation, however, is that in some situations, treatment breaks are introduced not because of toxicity or progression but to provide a period without chemotherapy (ie, chemotherapy holiday), although this can be handled by not considering these breaks as treatment failures. Another limitation is that early treatment discontinuations are still considered failures in situations where significant toxicity occurs, but patients have good disease outcomes (perhaps with improvement of toxicities) thereafter.

QoL-Related End Points

The main goal of cancer treatment, certainly in the palliative setting, should be to reduce discomfort related to or caused by cancer progression and its related consequences (eg, loss of functionality, inability to stay at home, deterioration of QoL). Health-related QoL (HRQoL) is a major concern for patients with cancer, and it can be affected by symptoms caused by cancer as well as by treatment-induced toxicity.[26] For many older patients, the goal of cancer-directed treatment is not just how much additional time they can gain but how valuable that time is. Elderly patients are less willing to compromise their HRQoL for the potential for increased survival.[27] Thus, HRQoL may be an appropriate outcome for elderly-specific trials, but it remains to be defined how to measure or quantify HRQoL optimally, how to quantify the different domains of HRQoL in one score, and which cutoffs are relevant as end points for clinical trials, although a 10-point decrease (on score of 100) is frequently used as relevant change.[28] The EORTC (European Organisation for Research and Treatment of Cancer) QoL Group recently developed an elderly-specific QoL module,[29] which adds specific QoL-related aspects in older individuals to the general EORTC Quality of Life Questionnaire C30. HRQoL should be captured in all trials of palliative chemotherapy in older patients regardless of the primary end point of the trial. The Q-TWIST (quality-adjusted time without symptoms of disease or toxicity of treatment) approach measuring quality-adjusted survival is another QoL-related end point, which partitions the survival time of the patient into three consecutive health states (ie, time with toxicity resulting from treatment, time without symptoms of disease or toxicity, and time from progression/relapse to death) and assigns utility weights to each state.[30] The Q-TWIST value is the sum of the weighted health state durations and is used for treatment comparisons. This approach quantitatively adjusts periods in which treatment toxicities or symptoms of disease progression are present to reflect the potentially reduced value for the patient. In principle, this is a valuable approach for older patients with cancer, but the great difficulty lies in determining or quantifying the weight factor for QoL during the different periods.

Preservation of Functional Capacity/Independence

In a similar way, maintenance of function and independence should be one of the major principles of cancer management in the elderly. A negative impact on a patient's functional capacity will have a negative impact on survival as well.[31] The prolongation of active life expectancy seems much more important than the prolongation of life expectancy as such. The GERICO (French Geriatric Oncology Group) trial[32] nicely showed that functionality measured by instrumental activities of daily living does not decrease significantly (by $\geq$ two points) in older patients with breast cancer receiving adjuvant chemotherapy. Using single or multiple domains of geriatric assessment as outcome events would also be of great value to clinicians.

Surgical Trial End Points

Several trials in the surgical field, including elderly-specific trials such as the PACE (Pre-operative Assessment of Cancer in the Elderly)

study,[33] have used (primary) end points such as 30-day morbidity, 30-day serious morbidity (grade 3 to 4), and 30-day mortality, which are relevant but should be accompanied by information on longer-term outcome end points, as we have discussed here.

TRIAL DESIGN IN OLDER PATIENTS WITH CANCER

Trials for Older Patients Versus Trials Without Upper Age Limit

Table 2 lists issues in clinical trial design in older patients with cancer. Clinical trials need to be representative of the whole population in whom the treatment will be used later, which is not the case at present. Several studies have shown that there is substantial underrepresentation of older patients in clinical trials.[10,34,35] The differential effects of aging on organ function and the variety of comorbidities that characterize the older population result in significant heterogeneity.[36] This variance could result in considerable differences in the efficacy and safety of cancer treatments. For studies using therapy regimens expected to be used in all age categories, patients should be enrolled across the entire age spectrum, and a minimum cohort of elderly patients should be required. If treatment regimens are expected to be tolerated by only fit older patients or younger patients, severe selection bias will be present, and conclusions from these kinds of trials will not be generalizable to the whole population, especially the frail elderly. It is important to capture the fitness status of the older patients enrolled onto a clinical trial to provide information about the generalizability of the results. Documentation of the nonincluded population is also important. One option for ensuring sufficient accrual of older patients could be to require registration trials to remain open after they have met their target accrual until a minimum cohort of elderly patients is enrolled. It should be noted that older fit patients are likely included in clinical trials and so should likely receive the standard treatments. However, it is clear that several standard treatments administered to younger patients are not suitable for unfit or frail elderly adults (and sometimes even fit elderly adults) because of expected higher or unacceptable risk of toxicity or other competitive risks determining the long-term prognosis. For example, allogenic bone marrow transplantation; high-dose cytarabine, anthracycline, or cisplatin; major surgery; and concurrent chemoradiotherapy are treatments generally reserved for younger or sometimes fit older patients. In this setting, elderly-specific trials are certainly needed, because there is no clear standard therapy in this group of patients, who are not likely to tolerate the standard therapy administered to fit patients. In frail older patients, separate clinical trials could be designed because these patients could be better served by trials comparing modified approaches (eg, adapted chemotherapy/biologic agents) with pure palliative/supportive care. For vulnerable patients, a possible trial design could include standard therapies versus less aggressive therapies or no therapy, depending on the setting.

Randomized phase III trials remain the gold standard for clinical research, in older as well as younger people. However, designing these trials that address heterogeneity in all elderly populations might be challenging for many reasons (insufficient interest from sponsors/investors, difficulty in finding sufficient numbers of patients, and so on). Often, phase III data exist only for younger populations. Randomized phase II trials can provide insight into the range of efficacy and toxicity in older populations. If the treatment is too toxic, this would be established in a phase II trial. If a phase II trial in an older (nonfit) population shows that the toxicity is acceptable and confirms efficacy in the same range as previous phase III trials in younger people, there might not be a need to repeat the phase III trial again in an older (nonfit) population. However, if the phase II results are indeterminate concerning toxicity and/or efficacy, then confirmation in a phase III trial is likely. Randomized phase II trials in specific subsets of older patients can thus potentially provide relevant information. In these cases, physical status (frailty and vulnerability) could be used as a stratification factor to explore the benefit of treatment in different older populations. Often, no real standards exist for this population (because standard therapy for that disease/indication is expected to be too intense for that person), and all treatments/study arms could actually be seen as experimental arms. Although it might be difficult to select a control arm in a randomized phase II trial, one possibility would be to make the control arm the physician's decision. Because of the methodologic difficulties of defining appropriate control arms for the reasons mentioned in this article, randomized phase II trials might sometimes turn out to be infeasible. A pragmatic option for frail patients could be to perform only single-arm phase II studies with toxicity as an end point, allowing indirect comparison of toxicity (and efficacy) with fit young/old populations from previous studies. This kind of study could provide relevant information if the appropriate end points (HRQoL, functionality, and so on) are included but would be scientifically much less robust than randomized phase II or III studies. Nevertheless, this type of study is sometimes the only feasible option, and regimens studied this way, such as the R-miniCHOP (rituximab plus low-dose cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen in patients age > 80 years with diffuse large B-cell lymphoma,[37] have been adopted in clinical care because higher-level data are lacking.

Table 2. Issues in Clinical Trial Design for Older Patients With Cancer

Issue
RCTs remain gold standard when possible
Clinical trials should preferably integrate whole age range, including fit and frail older individuals
Elderly-specific clinical trials in older patients with cancer are required if standard therapy is different from that for younger patients
Trials of treatment strategy comparing different strategies (eg, therapy *v* best supportive care) should be encouraged
Randomized phase II or even single-arm phase II trials in specific subsets of older patients can provide insight into range of efficacy and toxicity in older populations but ideally should be confirmed in large phase III trials, which might be hard to perform for various reasons (eg, insufficient interest from sponsors/investors, difficulty in finding sufficient numbers of patients)
Not all questions can be answered with randomized trials, and large observational cohort studies or registries in community can provide further insight for frail population with less selection bias (preferably in parallel with or linked to RCTs)
Comparable/uniform geriatric assessment should be integrated into future trials in geriatric oncology
Regulatory authorities should require evaluation of efficacy and safety of new drugs in older and frail patients as well as in younger patients

Abbreviation: RCT, randomized clinical trial.

Aging is a highly individualized process that results in several changes in organ function, affecting the pharmacokinetics of anticancer drugs.[38] These organ system changes may result in altered drug metabolism, with a major impact on treatment tolerability. For that reason, pharmacokinetic studies and phase I studies should be designed specifically for older patients. New drugs could, for instance, be studied in amended phase I studies in populations with higher levels of comorbidity or functional limitations in parallel with standard phase I trials or after the drugs have shown promising results in the general population. An approach in the same line is to design phase I/II–type trials with progressively increasing inclusion criteria. The regimen of interest is first administered to patients in good condition, then in cohorts with increasing levels of functional limitations or comorbidities. This would provide evidence-based thresholds for dose reductions or regimen changes. Risk indicators that could be used for this approach include the CRASH (Chemotherapy Risk Assessment Scale for High-Age Patients) score,[39] the CARG (Cancer and Aging Research Group) score,[40] or criteria such as those used in lymphoma studies.[41,42]

Although incorporating geriatric assessment into oncology trials is usually feasible,[43] the major obstacle to using this as a stratification or even randomization factor is the exact/optimal definition of frailty or vulnerability. Balducci and Extermann[44] formulated an operational definition of frail, fit, and vulnerable patients in 2000 that is commonly used in the oncology world but has significant shortcomings; unfortunately, 10 years later, it is still not clear which are the best criteria and tests to be used to make this stratification.

Trials of Treatment Regimens Versus Trials of Treatment Strategies Versus Observational Cohort Studies

Randomized trials of treatment regimens comparing treatment A versus treatment B can provide important information. The CALGB (Cancer and Leukemia Group B) 49907 adjuvant breast cancer trial, for instance, showed that classical adjuvant chemotherapy (AC [doxorubicin and cyclophosphamide] or CMF [cyclophosphamide, methotrexate, and fluorouracil]) was clearly superior to so-called soft chemotherapy with capecitabine.[45] New drugs also need to be tested specifically in the older population because specific adverse effects might occur that potentially change the toxicity/benefit ratio. The older population represents a huge potential market for the pharmaceutical industry, but the enhanced risk of toxicity as well as non–treatment-related adverse events that sometimes occur in older patients might lessen the enthusiasm of the industry to support such trials and might hamper drug development and registration.

Trials of treatment strategy comparing no treatment with treatment (eg, prostate cancer surgery or no surgery; breast cancer adjuvant chemotherapy or not) are some of the most important kind of trials that need to be performed. However, several challenges exist. Persuading a patient to participate in a trial of therapy versus no therapy is generally much more difficult than participation in a trial of treatment A versus B, and selection bias and crossover will occur. In the former situation, the impact of random assignment (eg, chemotherapy or not) on older patients is much bigger than in the latter situation (eg, chemotherapy A *v* B). There are possible trial designs that might make this more palatable to patients, such as a cluster randomization design or postrandomization (double) consent design (also called the Zelen design), but these designs are less rigorous because they rely on unverifiable assumptions (eg, patient referral patterns). For both of these approaches, patient consent is sought for the study after the patient already knows which treatment (if any) he or she would receive, removing the anxiety that impending random assignment may produce. Another aspect is that funding is much more difficult to obtain for treatment strategy studies, because there is generally no benefit for industry (on the contrary, the omission of treatment might be disadvantageous for industry). Several attempts at trials of treatment strategy have failed in the past because of these and other reasons, as was nicely demonstrated in the ACTION (Adjuvant Chemotherapy in Older Women) trial for early breast cancer.[46] It should be noted that problems of accrual to trials that compare different treatment modalities or the omission of treatment in one arm are the same for younger, fit populations. Although treatment strategy trials are difficult, it is important that work continue on developing and using alternative designs for these types of trials in the nonfit older population. There is no perfect solution for this, but one pragmatic strategy is to invest much more in large observational cohort studies in the nonfit older population[47] or even in registry studies in the community. If possible, they can be linked to randomized trials, allowing the capturing of the nonincluded population as well as the assessment of different treatments and strategies with regard to outcome. This integration of an RCT into a registry trial increases the quality of an RCT, because the patient selection is better described, and it is better known to which patient populations the results of the RCT can be generalized.

Incorporation of Geriatric Assessment Into Clinical Trials

Geriatric assessment has not been used often in previous clinical trials, but it should become more frequently required in the future. Without geriatric assessment information, it is impossible to evaluate which older individuals were included in a trial (eg, fit patients only or fit as well as frail patients), limiting extrapolation of the study data to the general older population. This should be mandatory in registration trials and elderly-specific trials and should be encouraged in all trials including older people. However, many different forms of geriatric assessment exist, which complicates comparisons across trials. It is important to agree on a (more or less) uniform or at least comparable evaluation of the older population. EORTC has made an attempt by providing a minimal data set for geriatric assessment to be included in clinical trials,[48] and CALGB has also demonstrated the feasibility of a mainly self-administered tool in its trials,[49] but there are other options,[41,42] and it is important to continue international discussion on this topic.

Eligibility Criteria

The generally long list of inclusion and exclusion criteria during the last decade has led to selection bias and exclusion of older patients. Exclusion criteria are not based on a high level of evidence. In clinical trials, especially those focusing on older patients with cancer, an attempt should be made to have as few inclusion and exclusion criteria as possible. A National Institutes of Health team concluded that decreasing function and comorbidity restrictions can dramatically increase elderly accrual to clinical trials.[34]

European Medicines Agency and US Food and Drug Administration Geriatric Investigation Plan

In the medical care of pediatric patients, the European Medicines Agency (EMA) has established a pediatric investigation plan to ensure that drugs are examined appropriately in the pediatric population. There is a need for a global strategy within the EMA/US Food and Drug Administration (FDA) to do the same in the older population. Compulsory use of uniform geriatric assessment and frailty tools in drug registration trials could be helpful in establishing a better view of the fitness of older patients included in clinical trials. The EMA/FDA could require adequate representation of older adults in registration trials if applicable (with information from geriatric assessment) or require postmarketing safety studies in the general older population. The EMA recently established a geriatric expert group for this purpose.[50] Longitudinal as well as baseline evaluation of geriatric parameters (eg, functionality, social situation, QoL) is crucial to better understanding the impact of new therapies on older individuals and to improving care for this important population.

DISCUSSION

Choosing end points for clinical trials in older patients with cancer requires careful reflection on the ultimate goals of therapies. OS is a crucial end point, but DSS should also be recorded in trials where older patients with cancer are included, because deaths resulting from other causes (eg, other diseases, treatment toxicity) occur much more frequently in the older population. Composite end points allow the integration of multiple dimensions in addition to efficacy (eg, QoL, evolution of functionality) into the definition of treatment benefit and have clear advantages in RCTs involving older patients with cancer, such as simplicity of statistical design and statistical efficiency. Composite end points are not feasible in all settings, but they are justified if the individual components of the composite are clinically meaningful and of similar relative importance to clinical care. QoL and preservation of functional capacity and independence are important for the older population and should be included more often as end points in clinical trials in this population.

Although clinical trials in principle should include the entire age range of the population, the heterogeneity of this population generally does not allow the capture of the whole older population, leading to selection bias and difficulty in drawing firm conclusions for the frailer elderly who are often not included. Specific trials for subgroups of older patients with cancer are needed, with additional pharmacokinetic studies if required, and with appropriate control arms depending on the setting. Randomized or single-arm phase II trials can provide insight into the range of efficacy and toxicity in older populations, but ideally they should be confirmed in large phase III trials that are unfortunately often hindered by insufficient interest from sponsors/investors or difficulty in finding sufficient numbers of patients. Large observational cohort studies in the nonfit older population should be considered, preferably linked to randomized trials, to capture the nonincluded population. Incorporation of a preferably uniform geriatric assessment in elderly-specific or registration trials is crucial to better understanding the effect of treatments in different elderly populations. Regulatory authorities including the EMA/FDA should require geriatric assessment information and adequate representation of older adults, including patients of different health statuses such as vulnerable and frail patients, in trials. Better clinical trial design is crucial to understanding the impact of new therapies on older individuals and to improving care for this important population.

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