

Advancing Treatment Approach to the Older Patient with Cancer Through Clinical Trials Participation



Efrat Dotan, MD

KEYWORDS

• Clinical trials • Elderly • Older cancer patients

KEY POINTS

- Treatment of older patients with cancer is challenging because of physiologic changes of aging, multiple comorbidities, functional decline, cognitive dysfunction, and limited social support.
- Older patients with cancer are poorly represented in clinical trials because of many barriers that limit their active accrual. Thus, limited data are available to guide the treatment approach to this patient population.
- Barriers to accrual of older patients to clinical trials include strict eligibility criteria, limited support from the treating physician, and patient-related factors.
- Decisions regarding clinical trial participation should be based on functional age rather than chronologic age. Older fit patients who are eligible for clinical trials should be encouraged to enroll.
- Elderly specific clinical trials, and studies evaluating a less fit patient population, are the gold standard for obtaining evidence that can guide oncologic treatment decisions in the clinic.

CANCER IN OLDER ADULTS

With the aging of the population there continues to be a steady increase in the number of older adults routinely seen in oncology clinics, and the challenges associated with the care for this patient population are encountered daily by oncologists worldwide. According to the US Census Bureau by 2050 the number of individuals older than age 65 is projected to surpass 80 million, representing about 20% of the population.¹ Age is known to be a risk factor for many cancers, it is estimated that 60% of the

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Department of Medical Oncology, Fox Chase Cancer Center, 333 Cottman Avenue, Philadelphia, PA 19111, USA

E-mail address: Efrat.Dotan@fccc.edu

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incidence of cancer and 70% of mortality from cancer occurs in patients that are older than the age of 65 (Fig. 1, Table 1).^{2,3} Life expectancy carries a significant weight when evaluating and treating older patients with cancer. With improvement in many areas of medicine, life expectancy continues to rise, with projection of an average of 20 years of living for 65-year-old individuals by 2050.¹ This results in a higher portion of older individuals that are seen in practices who are candidates for surgery, and other anticancer therapies. Patients older than the age of 65 accounts for the group that carries the highest personal health care spending in the United States, with continued increase in spending as individuals age.⁴

Surgeons and medical oncologists who are treating older patients with cancer are becoming more comfortable with delivering complex therapies to these individuals. This was demonstrated by Vijayvergia and colleagues⁵ who reported an increase in the number of older patients and patients with multiple comorbidities that receive multi-agent therapy for metastatic colon cancer over the last two decades. Similarly reports are seen in the literature describing complicated surgical procedures being safely performed on older adults.^{6–8} Yet controversy remains with regards to the tolerance of these treatments among older adults, with concerns of increased toxicity in this population. For example, a recent large registry study evaluated the outcomes of older patients with early stage colon cancer who underwent surgical resection. In that study, older age was associated with higher 1-year overall cancer-specific and cardiac-specific mortality.⁹ It is clear that age alone could not be used to determine the treatment approach in this patient population because multiple other factors influence the ultimate outcome. The treating physician is challenged daily with predicting

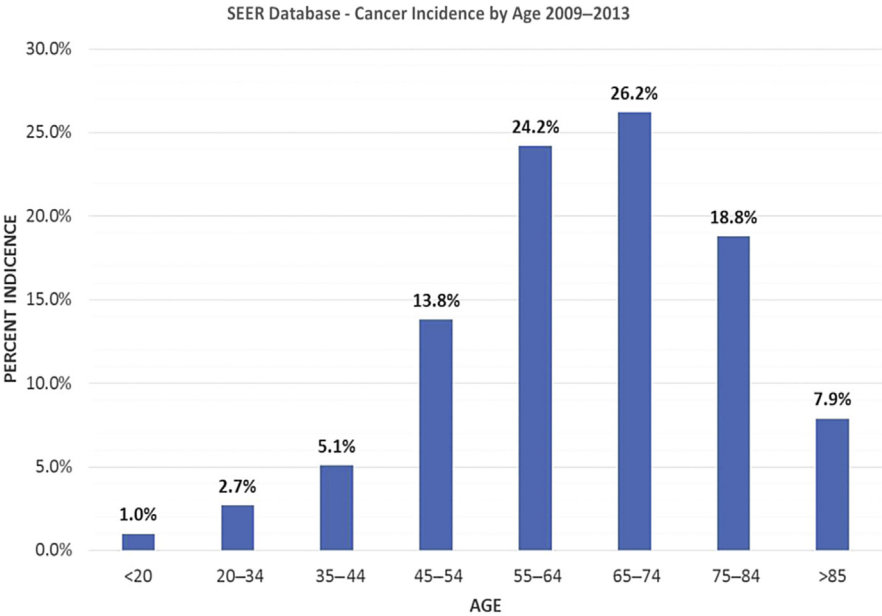


Fig. 1. Surveillance, Epidemiology, and End Results database statistics fact sheet: cancer incidence by age. (Adapted from Howlader N, Noone AM, Krapcho M. et al. SEER Cancer Statistics Review, 1975–2013. Bethesda (MD): National Cancer Institute; 2016. Available at: http://seer.cancer.gov/csr/1975_2013/. Based on November 2015 Surveillance, Epidemiology, and End Results data submission, posted to the Surveillance, Epidemiology, and End Results Web site; with permission.)

Table 1
Surveillance, Epidemiology, and End Results database statistics fact sheet: median age at diagnosis

Cancer	Median Age at Diagnosis
All cancers	65
Oral cavity and pharynx	62
Digestive system	68
Respiratory system	70
Breast	62
Female genital system	61
Male genital system	66
Urinary system	69
Lymphoma	65
Myeloma	69
Leukemia	66

From Howlader N, Noone AM, Krapcho M. et al. SEER Cancer Statistics Review, 1975-2013. Bethesda (MD): National Cancer Institute; 2016. Available at: http://seer.cancer.gov/csr/1975_2013/. Based on November 2015 Surveillance, Epidemiology, and End Results data submission, posted to the Surveillance, Epidemiology, and End Results Web site; with permission.

the ability of their older patient to undergo various anticancer therapies, and distinguishing between those who are fit and would benefit from these interventions, and those who are frail and are better served with less aggressive treatment approaches.

Physicians caring for older patients with cancer face multiple challenges. Most importantly, older patients have an altered response to many anticancer therapies compared with their younger counterparts. This is mainly caused by physiologic changes related to the aging process. Decrements in renal and hepatic function, altered gastrointestinal motility, loss of cardiac and marrow reserves, changes in cognition, and decrements in bone and muscle mass may increase the risk for treatment-related toxicity. Furthermore, the high incidence of comorbidities adds additional challenges to the planned therapy. The Centers for Disease Control and Prevention estimates that 80% of older adults have at least one chronic condition and 50% have two or more conditions that affect their care.¹⁰ The presence of multiple comorbidities results in patients receiving additional medications, and often dealing with the challenges of polypharmacy. The reported rate of polypharmacy among older patients with cancer varies in the literature, with one study reporting most patients receiving an average of eight medications.^{11,12} Finally, older patients often suffer from decrease in their performance status, and increased need for daily support from family members. Social support directly affects the patient's access to care, and ultimate treatment decisions. All these factors must be assessed before finalizing the treatment decision, and the proposed therapy should be personalized for each patient based on these factors. A comprehensive geriatric assessment (CGA) is the recommended tool for assessing these domains.^{13,14} It has been shown to be predictive of disease- and treatment-related outcomes, and unmask underlying disabilities that are not detected with a regular clinical assessment.^{15,16} Despite these data, the use of a CGA in routine oncologic practice remains low, and treating physicians rely more on their "eye ball" test rather than objectively collected information. Multiple screening tools have been developed that are easily implemented in an oncology clinic, and alert the physician for the need for a thorough geriatric evaluation.^{17,18}

PARTICIPATION OF OLDER PATIENTS WITH CANCER IN CLINICAL TRIALS

In addition to the previously mentioned challenges related to the aging process another pronounced challenge lies in the lack of clear evidence to guide the treatment decisions in this patient population. Clinicians are forced to extrapolate from data derived from studies conducted on younger and healthier patients when deciding on a treatment plan for their older patient with cancer. Older patients with cancer are significantly underrepresented in clinical trials evaluating new cancer therapies. A study by Hutchins and colleagues¹⁹ found that only 25% of patients enrolled on 164 Southwest Oncology Group studies were older than the age of 65, whereas 63% of patients with cancer were older than that age at the same time period. Similar findings were reported by Lewis and colleagues²⁰ who reviewed the rate of elderly patient participation in National Cancer Institute–supported clinical trials. In this analysis 32% of participants in phase II and III National Cancer Institute–supported studies were older than the age of 65. A more recent analysis evaluated the accrual of older patients with breast cancer to clinical trials run through the Alliance between 1985 to 2012. Similarly, the overall percentage of older patients enrolled on these studies was lower than that seen among the US breast cancer population. The odds of older patients enrolling on adjuvant studies increased over time, yet decreased over time for neoadjuvant and metastatic studies.²¹

The proportion of older patients participating in registration studies that ultimately result in the US Food and Drug Administration approval has also been shown to be low. Talarico and coworkers²² found only 36% of 28,000 participants in 55 such studies were older than the age of 65, a total of 20% older than the age of 70%, and 9% older than the age of 75. In comparison these subcategories encompass 60%, 46%, and 31% of the overall cancer patient population, respectively. A more recent analysis reviewed 24 new drugs that were approved between 2007 and 2010 for the treatment of cancer and found only 33% of participants in these studies to be older than the age of 65.²³ Regrettably, these data portray lack of progress in this arena and further deepen the gap of knowledge with regards to the treatment approach to this patient population. A recent position paper by the American Society of Clinical Oncology summarized these concerns and urged the oncologic community to take action in improving evidence-based care of the older patient population.²⁴

Multiple barriers to enrollment of older patients on oncologic clinical trials have been identified over the years. Overly restrictive eligibility criteria in studies are one of the main reasons for underrepresentation of this patient population in therapeutic studies. A study of 87 clinical trials in patients with non-Hodgkin lymphoma reported 25% of studies excluding patients older than the age of 65, and an additional 54% of studies excluding older adults through selective eligibility criteria aside from age.²⁵ With stringent eligibility criteria researchers limit the accrual of the “real-life” patients on studies and decrease the ability to learn and produce good evidence that can guide therapy. Multiple societies including the Institute of Medicine have called for the development of eligibility criteria that allow for the broadest participation possible.^{24,26}

Another common barrier to clinical trial enrollment lies in the discussion that the patient has with the treating physician. Treating physicians can be a major barrier to enrolling older patients on therapeutic studies out of concern for enhanced toxicities. Javid and colleagues^{27,28} found that when studies were available and patients were eligible, these studies were discussed more often with younger than with older patients (78% vs 58%). Conversely, studies have shown that age and comorbidities were not clearly predictive of toxicities on studies.²⁹ Rather than using chronologic age to determine if a patient is a candidate for a study, biologic and functional age

should guide this decision. Clinicians must be educated in appropriate assessment tools that can provide a full evaluation of the patient's overall function, and fitness for clinical trial participation. Those patients who are found to be fit for studies should be encouraged to participate in studies that would enhance the fund of knowledge.

Contrary to the assumption of many physicians, studies have shown that older patients view participation in clinical trials positively, and would be open to this option if given the choice.^{30,31} However, there are some patient-related factors that potentially limit participation of this patient population in clinical trials. Older patients fear the loss of autonomy over treatment choice, the loss of decision-making capacity, and the impact of any therapy on quality of life, all of which may occur while on studies. Other barriers include cultural differences in the attitude toward clinical trials, and the perception of the relatives of the benefit of such intervention.²⁷ Nevertheless, the recommendation from their treating physicians is rated as the highest factor to influence the decision of an older patient.³² With this in mind, physicians should be educated on having such discussions with an older patient with cancer, and encouraging eligible patients to participate in appropriate clinical trials.

ELDERLY SPECIFIC CLINICAL TRIALS

The need for better evidence to guide the therapy for older patients with cancer has been proclaimed by many national groups.³³ This provides a wide support for elderly specific studies evaluating anticancer therapies, supportive care measures, and assessment tools in this patient population. In addition to evaluating these interventions in fit older patients without any contraindication for therapy, such interventions should also be evaluated in frail patients to clarify the appropriate approach to individuals that cannot tolerate standard of care therapy. Furthermore, trial design and study end points may be different when conducting studies in this patient population. For example, evaluating the "active-life expectancy" (time where the individual remains active, lives independently without disability), and the treatment's effect on physical/cognitive functions is of higher interest in the older patient population in comparison with end points evaluating survival.

Different study designs have been implemented in an older patient population successfully. These studies serve as a model for future elderly specific clinical trials that would advance the field. Randomized controlled trials (RCT) are the gold standard evidence to guide the treatment approach, and those have been conducted in an older population. For example, the MILES study was a phase III RCT evaluating the use of single-agent versus combination chemotherapy in patients 70 years or older with newly diagnosed non-small cell lung cancer.³⁴ A similar study was CALGB 49907 conducted among older patients with breast cancer evaluating two forms of adjuvant chemotherapy.³⁵ Another recent study that highlights the ability to conduct elderly specific RCT is the AVEX trial, which enrolled patients older than the age of 70 with newly diagnosed metastatic colorectal cancer evaluating the benefit of the addition of bevacizumab to capecitabine.³⁶ The FOCUS2 study is an excellent example of an RCT conducted in an unfit older patient population that were not candidates for standard of care therapy.³⁷ The previous examples outline the feasibility of conducting RCT in elderly patients and unfit patients, and the high utility of the data derived from these studies.

Evaluating every new therapy in an older cohort of patients is not feasible. Therefore, a more attainable goal is to expand the age range of patients eligible for studies, and potentially stratify enrollment into age groups representative of the general population

with the cancer target of the trial.³³ This was modeled in the RCT that led to the approval of abiraterone for metastatic prostate cancer, where the median age of patients was 69 (range, 42–95; about 30% of patients older than the age of 75).³⁸ Supporters of elderly specific studies have also proposed a model of extended trial design with specific attention to the age distribution of the superior arm.³³ In this model, once an RCT is complete the superior arm is examined to ensure it had an age distribution that resembles that of the population with the specific disease. If this was not the case, that arm would then reopen and enroll a sufficient number of older adults. Another alternative is to conduct a phase IV study that would evaluate the new standard in the population of patients that was underrepresented in the registration study. These models are novel, and have not been implemented to date.

Single-arm studies are also a good modality to assess the benefit and toxicities of a certain drug or intervention. This type of study design allows for nontraditional end points that are of high importance in elderly specific studies. These models also inform tolerance to therapy and potential different dosing schedules that better serve the older patient population. An example for such study was the CALGB 9762, which evaluated the relationship between patients' age, paclitaxel pharmacology, and toxicity.³⁹ Another approach to evaluating the effect of a new treatment modality on an older patient population has been evaluating this population retrospectively following the approval of a new agent. An example for this is the BRITe registry, which collected data regarding tolerance of bevacizumab following its approval. Analysis of older adults who were included in this observational registry allowed us to draw information regarding the tolerance of this agent in the older patient population.⁴⁰ As is often the case in oncology, when prospective data are lacking retrospective studies fill the gap to provide additional guidance to the care of patients. Many therapies across different cancers have been studied retrospectively in older adults and these publications provide clinicians with some clinical guidance.^{41–44}

ADVANCING KNOWLEDGE ABOUT ASSESSMENT AND SUPPORTIVE CARE OF THE OLDER PATIENT WITH CANCER

Although clinical trials are crucial to advance knowledge and treatment approach to the older patient with cancer, continued evaluation of the optimal process of assessing older patients, and the optimal supportive care measures are of great value. In recent years, landmark studies have validated the importance of CGA in an oncology setting as a predictor of outcomes and toxicities.^{45–47} Additional studies have been conducted that define the most robust tool for screening older patients with cancer in a clinical setting, and identifying patients who would benefit from a full geriatric assessment.^{17,48} Finally, clinical models have been developed that assist the oncologist in predicting the risk for toxicities associated with chemotherapy in an older cancer population.^{49–51} Additionally, the ability to conduct these assessments through a World Wide Web-based patient self-reported assessment has been demonstrated as well.⁵² These data provide clear support for the benefit of a CGA in older patients with cancer; additional studies and physician education are needed to define the best way to incorporate these tools into clinical practice.

Because the aging population values quality of life and maintaining their functional status highly, and often over longevity, studies should evaluate supportive care measures that improve these domains. The appropriate dosing for treatment regimens is a commonly debated question among oncologists. Some believe in starting low and slowly intensifying therapy based on tolerance, whereas others believe in starting at standard dosing and dose reducing in the setting of adverse events. Elderly specific

studies can help answer these questions. Future studies evaluating various dosing schedules, and the risks associated with them stratified by a profile detected through a geriatric evaluation would be of high value. Evaluation of various supportive care measures including nutritional support, physical therapy, cognitive, and psychological support in the setting of cancer would enhance the care provided to these patients.

SUMMARY

Older patients comprise a large population of patients with cancer, yet they are significantly underrepresented in oncology-based clinical trials. Multiple barriers exist that result in the low accrual of older adults with cancer to studies. Principal investigators, treating physicians, and patients all contribute in different ways to these barriers. Nevertheless, the only way to advance the field and enhance the evidence that guides the care of older adults is through better clinical research that is geared to this patient population. Regulatory agencies and national funding organizations should emphasize the importance of age distribution that mirrors that of the general cancer population in clinical trials. Furthermore, incentives to encourage researchers to obtain elderly specific data would further enhance the applicability of these study results. The oncologic community must bring together different stake holders that focus on enhancing the inclusion of older adults in clinical trials, supporting elderly specific research initiatives, and continued physician education of the importance of this task.

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