Phase 1 Clinical Trials in the Elderly: Enrollment Challenges

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Abstract

Cancer mostly affects older adults. Despite the increased incidence of cancer among older adults, they are underrepresented in oncology clinical trials. Such trials can provide patients with early access to promising interventions. Clinical trials are changing the future of cancer treatments. This article provides advanced practitioners in oncology an understanding of potential barriers to enrollment of older adults in oncology clinical trials. This article also summarizes the literature comparing tolerance, toxicity, and clinical benefit in the elderly compared with the nonelderly. Enrollment of elderly patients is essential. It is therefore important to create strategies to increase their enrollment. Advanced practitioners, along with other members of the health-care team, play an important role to advocate for elderly patients in phase I clinical trials.

Cancer is the second most common cause of death in the United States, exceeded only by heart disease, and accounts for nearly one out of four deaths (American Cancer Society, 2018). Age is the greatest risk factor for developing cancer. Approximately 60% of people who have a diagnosis of cancer are 65 years old or older (Cancer.Net, 2019). By 2030, an estimated one out of five Americans will be over 65 years of age. Older persons are the fastest growing segment of our population. The increasing older population will have a profound impact on our country's health-care systems (Centers for Disease Control and Prevention, 2013).

The U.S. Food & Drug Administration (FDA) recommends grouping older adults in more discrete categories (2001). The National Comprehensive Cancer Network (NCCN) classifies senior patients into three categories: young-old (ages 65–75 years), old (ages 76–85 years), and oldest-of-old (over age 85 years; NCCN, 2019).

Treating older patients with cancer is a challenge to cancer care providers. Furthermore, enrolling older patients with cancer into clinical trials remains an even greater challenge. For this age group, data are limited in terms of pharmacokinetics, toxicities, and the effectiveness of cancer treatments when compared

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with younger populations (Zafar et al., 2011). The FDA requires that package inserts of approved products include a "geriatric use" section that provides pertinent information about the experiences of older adults with the drug (FDA, 2001). However, in recent years, two thirds of drugs approved by the FDA, including many hematology and oncology medications, lacked adequate efficacy and safety data for patients older than 65 or 75 (Hinshaw, Kapusnik-Uner, Zarowitz, & Matuszewski, 2013). With these challenges, evidence-based care does not exist to assist health-care providers in providing treatment for older patients with cancer.

Cancer clinical trials develop new mechanisms to prevent, diagnose, and treat patients. They are also responsible for providing effective supportive care interventions. Specifically, phase I clinical trials bridge the gap from the laboratory to the patient. The main objectives of phase I clinical trials are to assess safety and tolerability, establish the maximum tolerated dose, and, importantly, provide investigators an opportunity to observe for any evidence of antitumor activity of a new agent. Clinical trials can provide patients with early access to promising interventions.

Even with cancer clinical trials providing the future of cancer care, it is estimated that less than 10% of patients with cancer participate in a clinical trial (Al-Refaie et al., 2011; Institute of Medicine, 2010). One of the essential steps to any clinical trial is finding patients who are eligible candidates. According to an FDA analysis, older adults are underrepresented in oncology clinical trials, especially those over age 75, and even more so those over age 80. For those aged 75 to 79, the cancer incidence was 13%, with a clinical trial participation rate of 8%, and for individuals older than 80, 16% and 4%, respectively (Singh et al., 2017). In addition, an analysis of clinical trial data from the Surveillance, Epidemiology, and End Results (SEER) database from 2005 to 2015 reported that of approximately 224,766 cancer patients, older adults were underrepresented in the registration trials of new cancer therapies, especially those over age 75 (Singh et al., 2017).

BARRIERS TO ENROLLMENT

To increase the accrual rate of older individuals into early phase I clinical trials, it is essential to first know about the barriers to enrollment. Then, strategies to overcome these barriers can be developed. Barriers to clinical trial enrollment among older persons can be characterized into three groups (Table 1).

Patient-Related Barriers

The first category is patient-related barriers. Older adults with cancer have complex medical and social issues. The risk of comorbidities increases with age. Comorbidities bring about physiological changes and polypharmacy. The majority of clinical trials prohibit enrolling people with hematologic, renal, hepatic, and cardiac abnormalities. The physiological changes associated with aging lead to a decline in these organ functions. These comorbidities also lead to polypharmacy, which can then lead to possible drug-drug interactions. Most clinical trials require participants to be ambulatory and capable of carrying out their daily activities of living independently. Cognitive function and nutritional status can also decrease with age, thereby potentially disqualifying older adults from enrollment.

Logistical barriers may present another obstacle to enrollment in clinical trials among older patients. Participation in a clinical trial may require patients to travel to cancer or academic centers. Older individuals may have financial restrictions preventing them from traveling long distances. Other reasons for declining to enroll in

Table 1. Barriers to Clinical Trial Enrollment

Patient/family related

- Age-related physiological changes
- Significant comorbidities
- Polypharmacy
- Travel to a new cancer center
- Loss of continuity with their primary oncologist
- Time commitment for patient/family
- Financial concerns
- Myths related to clinical trials
- Patient perception

Health-care provider related

- Physician perception of the older adult
- Culture
- Increased time/communication
- Lack of information/evidence

Trial/protocol related

- Strict inclusion/exclusion criteria
- Inability to define functional status
- Lack of trials designated for the older adult

a clinical trial include concerns about things such as adverse events or family or friends who oppose participation. Family opposition to enrollment is a more important issue for older patients compared with younger patients (Denson & Mahipal, 2014).

Health-Care Provider–Related Barriers

Perceptions among physicians about age and clinical trial participation are multifactorial. One study pointed to physician fears of possible toxicity, the fact that the best treatment was not available in the clinical trial, and comorbidity interactions in the elderly as the main barriers to enrollment (Kemeny et al., 2003). Findings from another study demonstrated that, among patients who are eligible for a study, clinical trial participation was discussed with 76% of patients younger than 65 years of age and 58% of patients older than 65 years. Advanced age may deter oncologists from choosing intensive cancer therapy, even if patients are highly functional and lack comorbidities (Foster, Salinas, Mansell, Williamson, & Casebeer, 2010). In a survey of oncologists' perception of barriers to accrual to clinical trials, oncologists felt the most important barriers to older patient accrual were significant comorbid conditions, poor compliance, concerns for treatment toxicity, and difficulty meeting the eligibility requirements (Townsley, Selby & Siu, 2005). A systematic review of the literature was conducted to analyze barriers of participation of underrepresented populations in cancer clinical trials. It was concluded that physicians may not inform older patients about trials because of their perception that older patients with cancer will not tolerate experimental medications directed by the trials as well as younger patients (Ford et al., 2008).

Trial/Protocol-Related Barriers

In cancer clinical trials, there are other criteria that may preclude older patients from participating in a study. Generally, clinical trials do not limit eligibility based on age alone. The majority of clinical trials prohibit enrollment of individuals with hematologic, renal, cardiac, or pulmonary abnormalities. Although these are logical exclusion criteria, they limit elderly enrollment in clinical trials because older patients generally have a higher number of comorbidities than younger individuals. In multiple studies, trial ineligibility was the greatest barrier to clinical trial enrollment among older persons, with both patients and physicians perceiving this barrier as a major obstacle, and up to 60% of elderly patients who did not enroll in a clinical trial stating they failed to do so because of trial unavailability or ineligibility (Javid et al., 2012). Many clinical trials require participants to be either ambulatory or capable of self-care activities of daily living. The proportion of older patients was 22% lower in trials that excluded patients with mild or moderate functional status impairments than in trials that did not exclude these patients (Lewis et al., 2003).

TOLERANCE, TOXICITY, AND CLINICAL BENEFIT IN THE ELDERLY

A review of National Cancer Institute (NCI)-sponsored clinical trial cooperative group studies analyzed phase I dose escalation trials. The studies involved more than 500 patients older than 70 years of age and included hematologic and solid tumor patients. As one would expect, as age and dose level increase, the probability of toxicities can increase. It was reported that increased age was associated with a higher occurrence of dose-limiting toxicities (DLT); however, this risk remained within the accepted threshold for phase I trials (Schwandt et al., 2014). It was concluded that age bias should not be a factor in the enrollment of elderly patients to phase I clinical trials (Schwandt et al., 2014; Table 2).

The clinical research unit at H. Lee Moffitt Cancer Center and Research Institute analyzed 39 trials with a total of 1,162 enrolled study patients, of which 32.7% were 65 and older. Overall response rates between the elderly and younger groups were similar (15.2% vs. 13.1%), with comparable treatment-related mortality rates (1% vs. 0.9%, respectively; Mahipal et al., 2015). It was concluded that regardless of complex pharmacologic profiles and logistical issues involved in treating the elderly population, elderly patients did at least as well as their younger counterparts (Mahipal et al., 2015).

The University of Texas MD Anderson Cancer Center analyzed the clinical course of patients 65 years and older enrolled in their phase I clinical trials. During a 5-year period, 347 patients 65 years and older were evaluated for disease characteris-

tics, toxicities, survival, and response. Again, their results demonstrated that phase I clinical trials are well tolerated in patients 65 years and older (Subbiah et al., 2016). Patients ages 70 to 79 years had a greater risk of grade 3 to 4 toxicities when treated with combinations (> 2 drugs) compared

Table 2. Summary of Clinical Trials

Lead author	Institution	Years studied	Number of patients	Purpose	Recommendation
Schwandt (2014)	Cancer Therapy Evaluation Program	1995–2011	> 500 adults on phase I oncology trials, > 70 years of age	Analyzed relationship between DLT and age	There should be no age bias in enrollment for elderly in clinical trials.
Mahipal (2015)	H. Lee Moffitt Cancer Center	1997–2007	1,162 adults on phase I clinical trials, patients separated into transplantation group and nontransplantation group	Analyzed survival, response, toxicity, and treatment-related mortality rates with age	Elderly do at least as well as non-elderly. Recommend increasing the phase I enrollment of elderly patients.
Subbiah (2016)	The University of Texas MD Anderson Cancer Center	2004–2009	347 adults on phase I clinical trials, > 65 years of age	Analyzed disease characteristics, toxicities, survival, and response with age	Phase I clinical trials were well tolerated in patients older than 65 years of age. Recommend increasing the phase I enrollment of elderly patients.
Rowe (2014)	Cancer Therapy & Research Center at UT Health San Antonio	2009–2011	461 adults enrolled in phase I clinical trials, both solid and hematologic cancers; elderly defined as > 70 years of age	Analyzed the rate of completion of at least 12 weeks of treatment, incidence of adverse events, prevalence of comorbidities, functional status, and survival with age	Elderly had a higher percentage of reporting toxicity or self-withdrawal from treatment. Progression of disease was higher in nonelderly. No significant difference in hematologic toxicity, hepatotoxicity, and nephrotoxicity. Recommend increasing the phase I enrollment of elderly patients.
Subbiah (2018)	The University of Texas MD Anderson Cancer Center, Sarah Cannon Research Institute, Moores Cancer Center at University of California	2004–2013	1,489 adults, 278 of which were > 65 years of age	Compared 3 age groups: older adults (> 65 years), middle age (40–64 years), and AYA (15–39 years). All patients were on a phase I clinical trial receiving VEGF/VEGFR inhibitors.	Elderly patients were just as likely as younger patients to achieve a clinical benefit.
Buechel (2018)	University of Oklahoma Health Sciences Center, Ochsner Clinic Foundation	2010–2016	237 patients, with 22% of patients ≥ 70 years of age; all patients had gynecologic cancers	Analyzed toxicity and clinical benefit rate between elderly and nonelderly	Similar toxicity profiles and clinical benefit rate. With careful selection, elderly can participate in clinical trials.
Dockery (2017)	University of Oklahoma Health Sciences Center, Memorial Sloan Kettering Cancer Center	–	398 adults, 78 of which were > 65 years of age	Analyzed tolerability and toxicity of olaparib between different age groups	Tolerability and toxicity of olaparib is similar between women ≥ 65 years and < 65 years of age.

Note. DLT = dose-limiting toxicity; AYA = adolescent and young adult.

with monotherapy (Subbiah et al., 2016). Risk factors that may be predictors of a shorter time to treatment failure and overall survival included performance status higher than 1, thrombocytosis, more than 2 metastatic sites, and an elevated lactate dehydrogenase (Subbiah et al., 2016).

The Cancer Therapy & Research Center at UT Health San Antonio conducted a retrospective review of the outcomes of patients enrolled in phase I studies from 2009 to 2011. The objectives were to compare demographics, comorbidities, tolerance of chemotherapy, and reasons for withdrawal from study between the elderly and nonelderly. They reported no significant differences between the elderly and nonelderly in reported hematologic toxicities, hepatotoxicity, and nephrotoxicity. However, the elderly had a higher percentage of other toxicities (28.3 % vs. 8.7%) and self-withdrawal (10.9 vs. 6.8%) from the protocol. The authors acknowledged that the data did not include some events that could affect patients' quality of life (such as fatigue or peripheral neuropathy) and did not reveal factors that would explain why being elderly was significantly associated with not completing the study protocol. Progression of disease was significantly higher in the nonelderly (61.5% vs. 43.5%; Rowe et al., 2014).

A comparative analysis of participation and clinical benefit rate among patients on phase I clinical trials with VEGF/VEGFR inhibitors was conducted by The University of Texas MD Anderson Cancer Center and associated hospitals. Of 1,489 patients, 278 were 65 years and older. They analyzed response outcomes and clinical benefit (defined as stable disease for 6 months or longer), partial response, and complete response. Although elderly patients accounted for less than 20% of participants in the trials, those who participated were just as likely as younger patients to achieve clinical benefit (Subbiah et al., 2018).

Older patients with breast cancer remain largely underrepresented in cooperative group trials (Freedman et al., 2017). Freedman and colleagues (2017) examined the Alliance for Clinical Trials in Oncology systemic therapy breast cancer trials from 1985 to 2012. The clinical trials included chemotherapy in neoadjuvant, adjuvant, and metastatic settings. The review included 16 Alliance protocols, which enrolled 19,507 patients. They compared reason for therapy cessation for older patients (age ≥ 65 years) compared with younger patients (age < 65 years). Early protocol treatment cessation was more frequent in those over age 65 (50%) compared with those below age 65 (35.9%) across trials (Freedman et al., 2017). Although cessation of therapy occurred more frequently in those over age 65 with adverse events as compared with those below age 65 (7.9% vs. 6.4% overall; $p < .0001$), the differences were small (Freedman et al., 2017).

For gynecologic cancers, a retrospective analysis of patients enrolled in phase I clinical trials from 2010 to 2016 was reported by the University of Oklahoma. 237 patients were included, of which 22% were women 70 years of age and older (Buechel et al., 2018). Toxicities were defined as either grade 3 or 4 by Common Terminology Criteria for Adverse Events (CTCAE) 4.0. Older patients has similar grade 3 or 4 hematologic (21% vs. 16%, $p = .38$) and nonhematologic toxicities (26% vs. 29%, $p = .64$). Women 70 years and older discontinued treatment due to toxicity only 8% of the time (Buechel et al., 2018). Median survival was 13.0 and 10.3 months in the younger and older than 70 years groups, respectively ($p = .35$). 63% of patients 70 years and older achieved clinical benefit (Buechel et al., 2018).

Specifically among ovarian cancer clinical trials, women 70 years and older make up only 10% to 23% of all patients on study (Dockery, Tew, Ding, & Moore, 2017). Little data exist regarding tolerability and toxicity of therapy for recurrent disease for older women (Dockery et al., 2017). Dockery and colleagues (2017) studied the overall tolerability and toxicity of olaparib (Lynparza), a PARP inhibitor, among older (≥ 65 years) patients with recurrent ovarian cancer treated on eight prospective trials of olaparib. Of 398 patients included, 78% were 65 years and older. This study concluded that the tolerability and toxicity of olaparib capsules are similar between women older and younger than 65 years who were treated for advanced recurrent ovarian cancer (Dockery et al., 2017).

Despite the fact that enrolling elderly patients in clinical trials is challenging, these analyses demonstrate that patients 65 years and older have an acceptable toxicity profile and can achieve a clinical benefit. Chronological age is a poor mark-

er for tolerability of treatment. Advanced age of a patient alone should not justify exclusion from phase I clinical trials.

RECOMMENDATIONS TO INCREASE ENROLLMENT

Understanding the complexity of clinical trials can be difficult for all patients, regardless of age. Research staff need to understand the barriers that exists for elderly patients and be willing to spend time to educate elderly patients on the complexities that accompany trials (Table 3). Research staff need to articulate the importance of potential benefits of clinical trials by educating elderly patients and their families that older adults tolerate clinical trials as well as the nonelderly. A systematic and individualized approach needs to be used by a health-care team to assist with the logistical aspects of clinical trial participation.

For example, lack of transportation is a commonly cited reason for why patients do not enroll (Denson & Mahipal, 2014; Zafar et al., 2011). Lack of transportation to an academic medical center, which is usually located in a major city, can be a challenge. Moving clinical trials into the community setting, closer to their home, may help to increase enrollment. Creative approaches by the research staff to assist with transportation and collaborate with home health services should be employed.

Elderly participation in clinical trials relies greatly on health-care professionals. Both health-care provider bias and perception have been shown to be impediments to the enrollment of older persons in clinical trials. Therefore, it is critical to create a culture change among health-care professionals to boost enrollment (Umutyan et al., 2008). Several meta-analyses have shown that age should not be a factor in enrollment in trials because the elderly have done as well as their younger counterparts (Mahipal et al., 2015; Schwandt et al., 2014; Subbiah et al., 2016). Moreover, elderly patients enrolled in phase I trials had improved survival rates when compared with elderly patients who did not receive treatment during a phase I trial (Zafar et al., 2011). As more studies are published and presented, health-care providers' perceptions may change.

After an assessment of the patient's goals of treatment and desire to continue with therapy, health-care providers can utilize comprehensive geriatric assessment (CGA) tools to address specific issues related to the management of cancer. These tools can assist health-care providers in highlighting unidentified health problems, evaluating patients at higher risk for mortality, reviewing the risks and benefits of treatment, and assist in managing patients deemed to be at high risk for toxicity (Buechel et al., 2018). The benefits of a CGA are prolonged survival, prediction of those who may not benefit from treatment, prediction of mortality, cancer treatment tolerance, and aid in decision-making to help avoid over- and undertreatment of cancer (Overcash, Ford, Kress, Ubbing, & Williams, 2019). Comprehensive geriatric assessment tools can address many domains, including functional status, nutritional status, cognitive function, psychological status, and socioeconomic issues (Hurria et al., 2014). Health-care providers can utilize a single assessment tool or several depending on patients' needs (Table 4).

Among the American Society of Clinical Oncology's (ASCO) recommendations for improving evidence-based care for the elderly is to reevaluate restrictive eligibility criteria for clinical trials (Hurria et al., 2014). ASCO, in collaboration with the Cancer and Aging Research Group, National Institute on Aging, and the NCI, held a conference series to examine the level of evidence and identify the highest research priorities in geriatric oncology (Hurria et al., 2014). Efforts are underway to encourage sponsors to take a more rational approach to inclusion/exclusion criteria for clinical trials, with the hope to potentially relax certain laboratory requirements that encompass multiple

Table 3. Recommendations to Increase Clinical Trial Enrollment

Health-care provider related

- Use geriatric assessment tools to better define physiological age
- Increase health-care provider perception/communication and dispel myths related to clinical trials
- Allocate research staff to cater to the logistical needs of elderly patients

Trial/protocol related

- Develop creative trial designs
- Include endpoints that are important for the elderly (e.g., maintaining independence)

Table 4. Geriatric Assessment Tools

Domain	Assessment tool	Description	Possible interventions
Functional	Timed Up and Go	Evaluates gait and balance	Physical therapy, occupational therapy, exercise rehabilitation
	Activities of Daily Living	Explores 6 functions: bathing, dressing, toileting, continence, transferring, and feeding	Physical therapy, occupational therapy, exercise rehabilitation
	Instrumental Activities of Daily Living	Explores 8 items: shopping, food preparation, housekeeping, laundry, transportation, self-medication, ability to handle finances, and ability to use the phone	–
Psychological	Geriatric Depression Scale	Rates depression in the elderly (not to be used as a diagnostic tool)	Counseling, referral to social worker or psychiatry
Cognitive	Mini-Mental State Examination	Evaluates cognitive function	Assess ability to sign consent, involve family/caregiver support
Nutritional	Mini Nutritional Assessment	Identifies patients at risk for malnutrition	Nutrition consult

organ function as long as safety is not compromised (Hurria et al, 2014). Another recommendation is to establish more pertinent endpoints that center around what is important to the elderly. These can include maintenance of function and independence, time without symptoms, and quality of life (Hurria et al, 2014). Several study designs were proposed by Hurria and colleagues (2014) to fill the gaps in knowledge regarding cancer treatment in older and/or frail adults. For each trial design, possible advantages and limitations were outlined. For example, for randomized clinical trials, having a treatment arm that accrues only patients 65 years and older would require a large sample size.

CONCLUSION

Cancer is associated with aging. Adults who are 65 years and older account for the majority of people diagnosed with cancer. With our growing elderly population, the need for evidence-based practice guidelines is essential for optimal patient care. Medical breakthroughs could not happen without clinical trials. It is important for clinical trials to enroll all participants, young and old, thereby giving all patients an opportunity to treatment with the best outcome. The recruitment of elderly patients in phase I clinical trials remains a challenge. Barriers for enrollment of elderly patients need to be addressed. The use of geriatric assessment tools, creative clinical trial designs, and clinical trials that address endpoints important to the elderly can assist health-care providers in enrolling the elderly in clinical trials. Advanced practitioners in oncology are important members of the health-care team. They are in an excellent position to dispel myths related to participation of the elderly in clinical trials, assess patients' status by using CGA tools, and advocate for the enrollment of elderly patients in phase I clinical trials.

Disclosure

The authors have no conflicts of interest to disclose.

References

Al-Refaie, W. B., Vickers, S. M., Zhong, W., Parsons, H., Rothenberger, D., & Habermann, E. B. (2011). Cancer trials versus the real world in the United States. *Annals of Surgery, 254*(3), 438–442. https://doi.org/10.1097/SLA.0b013e31822a7047

American Cancer Society. (2018). Cancer Facts and Figures. Retrieved from https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf.

Buechel, M., McGinnis, A., Vesely, S. K., Wade, K. S., Moore, K. N., & Gunderson, C. C. (2018). Consideration of older patients for enrollment in phase 1 clinical trials: Exploring treatment related toxicities and outcomes. *Gynecologic Oncology, 149*(1), 28–32. http://doi.org/10.1016/j.ygyno.2017.11.021

Cancer.Net. (2019). Aging and cancer. Retrieved from https://www.cancer.net/navigating-cancer-care/older-adults/aging-and-cancer

Centers for Disease Control and Prevention. (2013). The state of aging and health in America. Retrieved from https://www.cdc.gov/aging/data/stateofaging.htm

Denson, A. C., & Mahipal, A. (2014). Participation of the elderly population in clinical trials: Barriers and solutions. *Cancer Control, 21*(3), 209–214. https://doi.org/10.1177%

2F1073274814021003 05
Dockery, L. E., Tew, W. P., Ding, D., & Moore, K. N. (2017). Tolerance and toxicity of the PARP inhibitor olaparib in older women with epithelial ovarian cancer. *Gynecologic Oncology, 147*(3), 509–513. https://doi.org/10.1016/j.ygyno.2017.10.007
Ford, J. G., Howerton, M. W., Lai, G. Y., Gary, T. L., Bolen, S., Gibbons, M. C.,...Bass, E. B. (2008). Barriers to recruiting underrepresented populations to cancer clinical trials: A systematic review. *Cancer, 112*(2), 228–242. http://doi.org/10.1002/cncr.23157
Foster, J. A., Salinas, G. D., Mansell, D., Williamson, J. C., & Casebeer, L. L. (2010). How does older age influence oncologists' cancer management? *Oncologist, 15*(6), 584–592. https://doi.org/10.1634/theoncologist.2009-0198
Freedman, R. A., Foster, J. C., Seisler, D. K., Lafky, J. M., Muss, H. B., Cohen, H. J.,...Hurria, A. (2017). Accrual of older patients with breast cancer to Alliance systemic therapy trials over time: Protocol A151527. *Journal of Clinical Oncology, 35*(4), 421–431. http://doi.org/10.1200/JCO.2016.69.4182
Hinshaw, T., Kapusnik-Uner, J., Zarowitz, B., & Matuszewski, K. (2013). Identifying knowledge gaps in the labeling of medication for geriatric patients. *Pharmacology & Therapeutics, 38*(9), 535–540.
Hurria, A., Dale, W., Mooney, M., Rowland, J. R., Ballman, K. B., Cohen, J. H.,...Mohile, S. G. (2014). Designing therapeutic clinical trials for older and frail adults with cancer: U13 conference recommendations. *Journal of Clinical Oncology, 32*(24), 2587–2594. https://doi.org/10.1200/JCO.2013.55.0418
Institute of Medicine. (2010). *Transforming Clinical Research in the United States: Challenges and Opportunities: Workshop Summary*. Washington, DC: The National Academies Press. https://doi.org/10.17226/12900
Javid, S. H., Unger, J. M., Gralow, J. R., Moinpour, C. M., Wozniak, A. J., Goodwin, J. W.,...Albain, K. S. (2012). A prospective analysis of the influence of older age on physician and patient decision-making when considering enrollment in breast cancer clinical trials (SWOG S0316). *Oncologist, 17*(9), 1180–1190. https://dx.doi.org/10.1634%2Ftheoncologist.2011-0384
Kemeny, M. M., Peterson, B. L., Kornblith, A. B., Muss, H. B., Wheeler, J., Levine, E.,...Cohen, H. J. (2003). Barriers to clinical trial participation by older women with breast cancer. *Journal of Clinical Oncology, 21*(12), 2268–2275. https://doi.org/10.1200/JCO.2003.09.124
Lewis, J. H., Kilgore, M. L., Goldman, D. P., Trimble, E. L., Kaplan, R., Montello, M. J.,...Escarce, J. J. (2003). Participation of patients 65 years of age or older in cancer clinical trials. *Journal of Clinical Oncology, 21*(7), 1383–1389. https://doi.org/10.1200/JCO.2003.08.010
Mahipal, A., Denson, A. C., Djulbegovic, B., Lush, R., Kumar, A., Juan, T. H.,...Sullivan, D. M. (2015). Effect of age on clinical outcomes in phase 1 trial participants. *Cancer Control, 22*(2), 235–241. http://doi.org/10.1177/107327481502200217
National Comprehensive Cancer Network. (2019). NCCN Clinical Practice Guidelines in Oncology: Older Adult Oncology. Version 1.2019. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/senior.pdf
Overcash, J., Ford, N., Kress, E., Ubbing, C., & Williams, N. (2019). Comprehensive geriatric assessment as a versatile tool to enhance the care of the older person diagnosed with cancer. *Geriatrics, 4*(2), 39. http://doi.org/10.3390/geriatrics4020039
Rowe, J., Sukeshi, P., Mazo-Canola, A., Parra, A., Goros, M., Michalek, J.,...Karnad, A. (2014). An evaluation of elderly patients (≥70 years old) enrolled in phase I clinical trials at University of Texas Health Science Center at San Antonio-Cancer Therapy Research Center from 2009 to 2011. *Journal of Geriatric Oncology, 5*(1), 65–70. https://dx.doi.org/10.1016%2Fj.jgo.2013.08.005
Schwandt, A., Harris, P. J., Hunsberger, S., Deleporte, A., Smith, G. L., Vulih, D.,...Ivy, S. P. (2014). The role of age on dose-limiting toxicities in phase I dose-escalation trials. *Clinical Cancer Research, 20*(18), 4768–4775. https://dx.doi.org/10.1158%2F1078-0432.CCR-14-0866
Singh, H., Kanapuru, B., Smith, C., Fashoyin-Aje, L. A., Myers, A., Kim, G.,...Pazdur, R. (2017). FDA analysis of enrollment of older adults in clinical trials for cancer drug registration: A 10-year experience by the U.S. Food and Drug Administration [Abstract 10009]. *Journal of Clinical Oncology (ASCO Annual Meeting Abstracts), 35*(15 suppl). https://doi.org/10.1200/JCO.2017.35.15_suppl.10009
Subbiah, I. M., Tang, C., Rao, A., Falchook, G. S., Subbiah, V., Tsimberidou, A. M.,...Hong, D. S. (2018). Older adults in phase I clinical trials: A comparative analysis of participation and clinical benefit rate among older adults versus middle age and AYA patients on phase I clinical trials with VEGF/VEGFR inhibitors. *Oncotarget, 9*, 28842–28848. https://doi.org/10.18632/oncotarget.25571
Subbiah, I. M., Wheler, J. J., Hess, K. R., Hong, D. S., Naing, A., Fu, S.,...Tsimberidou, A. M. (2016). Outcomes of patients >65 years old with advanced cancer treated on phase I trials at MD Anderson Cancer Center. *International Journal of Cancer, 140*(1), 208–215. https://doi.org/10.1002/ijc.30417
Townsley, C. A., Selby, R., & Siu, L. L. (2005). Systemic review of barriers to the recruitment of older patients with cancer onto clinical trials. *Journal of Clinical Oncology, 23*(13), 3112–3124. https://doi.org/10.1200/JCO.2005.00.141
U.S. Food & Drug Administration. (2001). Guidance for industry: Content and format for geriatric labeling. Retrieved from https://www.fda.gov/media/72141/download
Umutyan, A., Chiechi, C., Beckett, L. A., Paterniti, D. A., Terrell, C., Gandara, D. R.,...Chen, M. S. (2008). Overcoming barriers to cancer clinical trial accrual: Impact of a mass media campaign. *Cancer, 112*(1), 212–219. https://doi.org/10.1002/cncr.23170
Zafar, S. F., Heilbrun, L. K., Vishu, P., Jasti, P., Venkatramanamoorthy, R., Ding, L.,...Heath, E. I. (2011). Participation and survival of geriatric patients in phase I clinical trials: The Karmanos Cancer Institute (KCI) experience. *Journal of Geriatric Oncology, 2*(1), 18–24. https://doi.org/10.1016/j.jgo.2010.09.004