editorials

Bridging the Data-Free Zone: Decision Making for Older Adults With Cancer

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Medical students and trainees are educated in the principles of evidence-based medicine. Trainees dutifully characterize trial populations, recognizing that one cannot generalize results to populations not represented in the study. However, quickly upon becoming physicians, particularly oncologists, they enter the "data-free zone," where the majority of patients in their office do not reflect clinical trial populations.[1,2] Although 2 out of 3 new cancers occur in older adults, this population only accounts for 30% of clinical trial enrollment.[1,3] The reasons for the disconnect between age of patients in the real world and clinical trials are multifactorial. First, although most trials do not explicitly exclude patients based on age, older adults are more likely to have comorbid conditions and reduced performance status when compared with their younger counterparts. Thus, older adults are more often ineligible for clinical trials.[3,4] Removing exclusion criteria related to organ dysfunction (cardiac function, hypertension, and hematologic and pulmonary function) and functional status could double the expected rate of clinical trial participation for older adults.[3] Second, older adults are less likely to be asked by their oncologists to participate in trials than younger patients. One study found that older patients with stage II breast cancer were less likely to be offered a clinical trial when compared with patients younger than age 65 years (34% *v* 68%, respectively). However, when offered to participate, older patients had similar rates of trial enrollment as younger patients.[5] Previous studies have cited various reasons for low enrollment of older adults in clinical trials, including concerns about the toxicity of treatment, presence of nonexclusionary comorbidities, concerns regarding potential noncompliance as a result of misunderstandings of complicated trial regimens, belief that the best treatment is not available in the trials, and lack of awareness about trial eligibility.[5,6] Although these concerns are both common and understandable, the limited participation of older adults in trials results in a lack of evidence to inform optimal strategies for the treatment of older adults.

Patients and oncologists are forced to make decisions within this data-free zone on a routine basis. This contributes to the prescription of nonstandard treatments in older adults, particularly omitting or decreasing chemotherapy.[7,8] One study of patients receiving adjuvant breast cancer treatment found that chemotherapy was recommended in 92% of chemotherapy-eligible patients age 50-59 years compared with 23% of chemotherapy-eligible patients age 70 years or older.[8] In our recent SEER-Medicare analysis of women with early-stage and metastatic breast cancer age ≥ 65 years old, we found that almost 20% of patients received an initial treatment that was discordant with national guidelines.[9-11] Common guideline deviations included trastuzumab without chemotherapy, single-agent bevacizumab, and single-agent chemotherapy in the adjuvant setting.[9-11] This use of nonstandard de-escalation strategies, which are less intense than standard of care, is problematic because of the lack of supporting evidence for use in patients with breast cancer. Previous research evaluating chemotherapy intensity indicates that older adults benefit from standard-of-care adjuvant therapy. A landmark study by Muss et al[12] evaluated capecitabine, as a less toxic chemotherapy choice, compared with standard chemotherapy of physician's choice (either cyclophosphamide, methotrexate, and fluorouracil or cyclophosphamide and doxorubicin) in adults age 65 years or older with early-stage breast cancer. Investigators halted the study prematurely when an interim analysis demonstrated increased risk of recurrence and death with capecitabine alone. In the 10-year follow-up of this study, overall survival was 62% for patients receiving standard-of-care chemotherapy compared with 56% for patients receiving capecitabine alone (adjusted hazard ratio [HR], 0.84; 95% CI, 0.66 to 1.07).[12] In another population-based study of patients with breast cancer in Switzerland, striking mortality differences were observed. Patients ≥ 80 years old who received breast-conserving surgery and adjuvant chemotherapy had a 90% decreased hazard of 5-year breast cancer–specific death compared with patients who did not receive any treatment (adjusted HR, 0.1; 95% CI, 0.03 to 0.4).[13] Thus, although nonstandard reduced-intensity treatment is likely prescribed with the best intentions, failure to prescribe standard therapy as a result of patient age may unintentionally result in the denial of best possible outcomes.

Although these studies highlight benefits of standard chemotherapy treatments in older adults, less is known about the use of novel targeted agents in this

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population. In the article that accompanies this editorial, Howie et al[14] should be applauded on their effort to fill this important knowledge gap through their investigation of the impact of novel therapy (CDK4/6 inhibitors) on survival. Their meta-analysis found that patients with metastatic breast cancer age 75 years or older derive similar benefit from CDK4/6 inhibition compared with that observed in patients younger than age 75 years (HR, 0.49; 95% CI, 0.31 to 0.76).[14] The results from this study support prior literature noted earlier, emphasizing the importance of considering standard therapies for all patients, including older adults.

Although the survival outcomes in the study by Howie et al[14] were excellent for adults age 75 years or older, the study also should provide the oncology community with cautionary considerations about how these results are applied to older adults. Compared with younger patients, older patients in this study were more likely to report toxicity, require dose modifications, and experience declines in quality of life. Most importantly, older adults receiving CDK4/6 inhibitors experienced a greater decline in their ability to perform usual activities.[14] These are not trivial findings. Older adults often prioritize preserved function and cognition over survival.[15] In a large study of $>$ 700 patients with advanced cancer, only 18% preferred length of life over quality of life, 55% weighed length of life and quality of life equally, and 27% preferred quality of life.[16] In a different study of older adults with cancer, the majority of patients preferred shortened survival over the loss of ability to care for themselves.[17] Therefore, survival gains in this study must be balanced against increased toxicity and declines in ability to perform usual activities for individual patients who may prioritize function over survival.

Unfortunately, data on the important outcomes that patients prioritize during treatment decision making are infrequently collected in clinical trials, which results in barriers to true shared decision making. Patient-reported outcomes are often underfunded and not prioritized as a central component of trials.[18] As a result, limited survey instruments are administered to patients within clinical trials. The most commonly used patient-reported outcome in clinical trials, health-related quality of life, is a useful composite end point. However, this can be difficult for patients to interpret and put into context of their lives when making decisions about treatment. What does a 5-point shift in health-related quality of life truly mean? Data on how treatments will affect day-to-day life would be more valuable for patients.

The field of geriatric oncology has begun to unpack this question through the use of the geriatric assessment, a validated tool designed specifically for older adults. This systematic and comprehensive assessment characterizes functional status, physical performance, falls, cognition, nutrition, comorbidity, social support, and psychological status.[19] This information is substantially more useful, both to providers and patients, in understanding study populations than either chronologic age or performance status. Hence, this tool should be included in clinical trials that enroll older adults, so clinicians can adequately assess the representativeness of clinical trial populations to their own patients.[2] Furthermore, the geriatric assessment can aid in distinguishing patients who may benefit from standard cancer treatment, as well as potentially guide nononcologic interventions.[20,21] When used throughout treatment, the geriatric assessment can also provide the clinical team an opportunity to identify when older adults are declining in function and to intervene to manage patient needs.[20,22] In a recent study by Pergolotti et al,[23] geriatric assessment was used to identify older adults with cancer and rehabilitation needs, and intervention participants reported improvements in self-efficacy and activity expectations. Moreover, a novel composite end point called overall treatment utility has been developed that incorporates multiple facets of successful treatment pertinent to older adults, including patient acceptability, preserved function (defined using the geriatric assessment), lack of toxicity, and radiographic response.[19] In their seminal work, Seymour et al[24] used overall treatment utility to demonstrate a benefit of the addition of oxaliplatin to fluorouracil in frail older adults. Thus, these tools have the potential to play a critical role in trial design, interpretation of results, and management of older adults with cancer.

ASCO and the US Food and Drug Administration have called for broadening clinical trial enrollment criteria as a result of the limited generalizability of trial results and the difficulties interpreting the risk-benefit ratio of a regimen in real-world settings.[25] We fully support this sentiment but would propose to take this a step further. We advocate not only for developing strategies to include older adults in clinical trials, but also for measuring outcomes that are meaningful for this unique patient population. Without such mechanisms to address the data-free zone and generate high-quality evidence for care delivery, we cannot minimize both the mortality and the morbidity of our older patients.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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