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Is the Lack of Evidence in Older Adults with Cancer Compromising Safety?

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1. Introduction

Cancer is predominantly a disease of aging, with more than half of all cancer diagnoses and more than two-thirds of all cancer-related deaths involving older adults [1]. Older patients with cancer differ significantly from younger patients with cancer given their increased heterogeneity, as they have been found to have lower self-rated health scores, more limitations in functional status, and increased incidence of geriatric syndromes and frailty [2]. Geriatric syndromes, such as falls, pressure ulcers, cognitive decline, depression, anorexia, sarcopenia, polypharmacy, and incontinence, are unfortunately common in this population and further complicate cancer care for older adults. Chronological age and performance status do not adequately capture these vulnerabilities. Furthermore, a cancer diagnosis can result in worsening and/or acceleration of many geriatric syndromes, as recently was demonstrated with regard to sarcopenia compared to a non-cancer control [3]. As the number of older adults with cancer continues to increase, the need to tailor all aspects of cancer therapy, from screening, diagnosis, and treatment, to supportive care and survivorship, will continue to be of utmost importance.

2. The Lack of Evidence from Clinical Trials

Unfortunately, there continues to be a knowledge gap regarding how to optimally provide cancer care in older adults, and we lack data on the benefit/risk balance for many treatment strategies in these patients [4]. For a number of reasons, such as clinical trial age restrictions, the presence of comorbid conditions, reduced functional status, and reduced access to resources, older adults with cancer are all too frequently not enrolled in clinical trials [5]. Despite representing the majority of cancer cases, older adults represent less than a third of

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clinical trial participants [5]. As a consequence, the medical community is providing cancer care to older adults based off of evidence that was acquired from an entirely different population - typically younger, healthier patients, often with less comorbidities and polypharmacy and different physiology. Therefore, despite the best efforts and intentions of the medical community, we are unfortunately often providing sub-standard care to older adults with cancer, leading to suboptimal care and potentially compromised safety for the growing number of older adults with cancer [4]. The lack of evidence surrounding many cancer treatment decisions likely contributes to nonstandard treatments and guideline deviations in older adults, particularly the omission or decreasing chemotherapy, but may similarly contribute to over treatment as well [6].

3. Drug Safety and Potential Harm in Older Adults

Drug safety is of particular concern amongst all older adults, as the potential problems of polypharmacy, medication interactions, and medication non-adherence are often more common amongst older adults. Polypharmacy is a common problem in older adults with cancer, as up to 50–80% of older adults with a new diagnosis of malignancy have been found to take at least five medications [7]. It is also important to note that polypharmacy can also be defined by the presence of “potentially inappropriate medications” for the older adult, which are those medications that have been associated with an increased risk of adverse outcomes in older adults. For example, in a review of 500 older patients with cancer undergoing chemotherapy, up to 29% of patients using “potentially inappropriate medications” as defined by the Beers criteria [8]. As such, medication interactions are another serious concern amongst older adults with cancer, as polypharmacy has been associated with an increased risk of adverse events, functional decline, and greater healthcare costs [7]. Moreover, age-related declines in renal and hepatic function as well as sarcopenia may substantially impact drug clearance and distribution, potentially contributing to large inter-individual variability in chemotherapy toxicity and tolerability [9].

4. Addressing the Need

Due to the concern for the complexity and difficulties in treating older adults with cancer, the Food and Drug Administration (FDA) and American Society of Clinical Oncology (ASCO) held a joint meeting in November 2017, seeking to address the knowledge gap in the care of older adults with cancer [10]. The joint FDA-ASCO meeting proposed four action items aimed at closing the gaps in knowledge in the care of older adults with cancer, including increasing clinical trial enrollment, making clinical trial information more readily available, augmenting the use of real-world data, and encouraging changes in policy. Specific recommendations from the meeting include: altering clinical trial eligibility criteria to include patients with medical comorbidities and organ dysfunction; increasing clinical trial options outside urban academic medical centers; creating clinical trial endpoints that are meaningful to older adults; increasing the use, documentation, and billing of geriatric assessments in the care of older adults.

To continue the groundwork laid out at previous meetings, the FDA is currently working on drafting industry recommendations to address this deficit – *Inclusion of Older Adults in*

Cancer Clinical Trials [11]. This document encourages broadening the participation of older adults in clinical trials, with the goal of enhancing the applicability and transferability of clinical trial results to the patients in our clinics. In addition to specifically seeking to augment the participation of older adults in clinical trials, the FDA has previously released a draft of industry guidelines aimed at increasing the participation of patients in clinical trials with medical comorbidities (*Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies* [12]).

Furthermore, in response to the growing population of older adults with cancer, as well the multitude of unique problems facing older adults and those providing care to older adults with cancer, the National Comprehensive Cancer Network (NCCN) has also published a separate set of guidelines for “Older Adult Oncology.” These guidelines cover a wide-range of evidence-based topics to assist in the care of older adults with cancer, including evaluation, considerations during cancer therapy, life expectancy, communication, geriatric assessment, and assessment of geriatric syndromes. These guidelines are frequently updated and are also readily available for use in the oncology community.

5. Expert Opinion

As each older adult is unique in their course amidst the aging process and regarding their preferences, goals, and circumstances, their oncologic treatment should similarly be personalized [13]. However, it is critical to use systematic assessments as part of routine care to guide such decisions and to better estimate treatment outcomes to make informed cancer decisions. The lack of inclusion of older adults in clinical trials has led to a knowledge gap in treatment outcomes. Moreover, few trials to date have incorporated the systematic assessments of patient cohorts required to make personalized decisions. Geriatric assessments should not only be used in the routine clinical care of older adults with cancer, but are desperately needed in clinical trials to better interpret results and decide which patients may benefit from specific treatments. These assessments do not have to be overly burdensome, and a comprehensive patient-reported geriatric assessment can be completed in as little as 10 minutes and provide a wealth of health information [14]. At the University of Alabama at Birmingham, we have pioneered the routine incorporation of the Cancer and Aging Resilience Evaluation (CARE) survey that is a brief and focused, yet comprehensive in scope, geriatric assessment, based on the Cancer and Aging Research Group (CARG) geriatric assessment, that is completed by the patient or caretaker at their initial visit to the medical oncology clinic [14]. Similarly, an international initiative developed a shortened geriatric core dataset (G-CODE) for use in clinical research involving older patients with cancer [15]. These surveys include information on functional status, nutrition, mental health, social support, comorbidities, health-related quality of life, and polypharmacy. The incorporation of this information and clinical trials will be critical in helping to bridge the knowledge gap in the care of older adults with cancer.

Moreover, the outcomes that older adults often value most are not typically represented in clinical trials. Clinical trials often report progression free survival, overall survival, and rates of toxicities, but most often older patients (as well as many younger patients) want to know how such treatments will impact their quality of life and functional independence. To make

the most informed treatment decisions, patients need to know how treatments will affect their day-to-day life. Routine incorporation of measures of health-related quality of life, function, and the use of novel composition outcomes that capture multiple facets of successful treatment would greatly improve decision-making in older adults with cancer.

Lastly, future studies are desperately needed that focus on pharmacologic monitoring of many common chemotherapeutics as the heterogeneity of this growing population likely results in widely variable pharmacokinetics and pharmacodynamics that go unaccounted for in current practice. In particular, the routine dosing of chemotherapy by body surface area (BSA) completely ignores changes in skeletal muscle and increases in adiposity as seen with aging [9]. Developing novel personalized dosing strategies based on the pharmacokinetics of cancer therapies could reduce unnecessary toxicities and improve outcomes for this vulnerable population.

In conclusion, continued efforts to improve the evidence base for the management of the growing number of older adults with cancer is warranted. Although there is undoubtedly increased recognition and some progress in these efforts, widespread changes are needed in the design and recruitment of ongoing and future clinical trials to close these gaps.

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Article Highlights:

- Most of the burden of cancer diagnoses and cancer-related deaths occurs in older adults.
- The number of older adults with cancer is projected to continue to increase over ensuing decades.
- Older adults are often excluded from clinical trial enrollment in oncology, leading to a lack of data on how to optimally provide cancer care for this population.
- Consequently, drug safety is an area of particular concern, as polypharmacy, medical comorbidities, and changes in physiology all influence cancer therapy and outcomes in older adults.
- There is a tremendous effort in the field of geriatric oncology to bridge this knowledge gap and to provide high-quality, evidence-based care for older adults with cancer.