A coming of age for immune checkpoint inhibitors in cancer

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Cancer & aging

Older adults represent a rapidly growing population in oncology, and they frequently present with complex concurrent medical issues [1]. Oncologists often encounter challenges when caring for older adults with cancer due to their multifaceted constellation of medical and psychosocial issues. Notably, studies suggest that older patients with cancer experience worse survival outcomes compared with younger patients, possibly due to suboptimal treatment [2,3]. Importantly, although data support that older adults derive similar benefits from chemotherapy compared with younger patients, older patients also have greater risk for experiencing side effects from chemotherapy, which may diminish oncologists' enthusiasm for offering such treatment to the geriatric oncology population [4,5]. Indeed, oncologists often seek more tolerable treatment options that can benefit older patients while avoiding unwanted side effects [6,7]. Older patients' increased toxicity from chemotherapy may be related to concomitant comorbid conditions, greater risk of polypharmacy, diminished functional reserves and lack of social support [5]. However, not all older adults have the same risk of experiencing poor outcomes and some may do well with treatment, thus reflecting a population with unique and varied needs [6,8].

Cancer & immune checkpoint inhibitors

In recent years, immunotherapies directed against negative regulators of the immune response have revolutionized the treatment paradigm for many patients with cancer. In particular, monoclonal antibodies targeting the programmed cell death 1 receptor (PD-1) and its ligand, PD-L1, have exhibited impressive activity across an evergrowing list of malignancies. Indeed, within a matter of just 5 years, PD-(L)1 inhibitors have become standard therapies in > 10 indications, ranging from melanoma to non-small-cell lung cancer to lymphoma. Currently, six PD-(L)1 inhibitors have gained regulatory approval in the USA, and there are ongoing efforts to expand the use of these agents to other malignancies and new disease settings (e.g., adjuvant therapy). In parallel, attempts to develop more effective immune-based combinations have become a major research focus throughout oncology.

Enthusiasm for the use of PD-(L)1 inhibitors stems from robust data demonstrating that these agents can induce significant, and sometimes durable, anti-tumor immune responses [9]. In general, PD-(L)1 inhibitors also have a more favorable side-effect profile compared with traditional cytotoxic chemotherapy [10]. Nonetheless, immune checkpoint inhibitors may also give rise to a unique spectrum of toxicities, known as immune-related adverse events (irAEs). While most irAEs are relatively mild to moderate, and transient in nature when promptly recognized, severe and/or even fatal toxicities have been observed. This has prompted ongoing efforts to develop consensus guidelines for the management of irAEs. Collectively, these trends underscore that the use of immunotherapy in everyday clinical practice will continue to expand and oncologists will need to be prepared for their growing use.

Aging & immune checkpoint inhibitors

Older adults represent the largest group of patients with cancer; thus, it is critical to understand the risks and benefits of novel cancer treatment in the geriatric oncology population [1,11]. Historically, older adults are underrepresented in cancer clinical trials despite their representation as the most commonly encountered patient in routine clinical practice [12]. Reasons for the underrepresentation of older adults in cancer clinical trials are myriad and include issues related to trial availability, rigid inclusion/exclusion criteria and even oncologists' hesitancy to discuss clinical trials with older patients. For these reasons, the evidence for how best to care for the rapidly growing geriatric oncology population is limited. Specifically, the data for using novel immunotherapy agents to treat older patients with cancer are sparse and limited largely to meta-analyses and retrospective studies [13–16].

Most of the available evidence for treating older patients with immune checkpoint inhibitors suggests that older adults with cancer experience clinical benefits. A meta-analysis investigating the benefits of checkpoint inhibitors in older adults with cancer age 65 and above identified 53 articles, 17 of which employed a randomized controlled study design [15]. Out of the studies included in this meta-analysis, various cancer types were represented, and multiple immune checkpoint inhibitors were used (e.g., nivolumab, pembrolizumab and atezolizumab). Importantly, improvements in overall survival were consistent for patients older and younger than 65 years who were treated with immune checkpoint inhibitors. Recently, Nishijima and colleagues performed a similar meta-analysis of nine randomized controlled trials, again with varying cancer types, to examine the impact of age on outcomes with CTLA4 (ipilimumab and tremelimumab) and PD1 inhibitors (nivolumab and pembrolizumab) [16]. This study also demonstrated that immunotherapy resulted in significantly improved overall survival in both younger and older patients. An important limitation of both analyses is the lack of details on tolerance and toxicity of immunotherapy in older adults.

To complement the above meta-analyses, several recent retrospective studies have been performed among older patients treated in real-world practice. One study focused on patients with melanoma and investigated the impact of age on survival outcomes and rates of immune-mediated toxicities in patients treated with anti-PD-1/anti-PD-L1 monoclonal antibodies at two academic medical centers [13]. Although this was a retrospective study, this work included broad age ranges to help clinicians understand differences across subgroups of ages: < 50, 50–64, 65–74 and ≥75 years. Importantly, this study demonstrated that immunotherapy has the potential to provide beneficial effects in patients with advanced melanoma independent of age. Moreover, the investigators also studied adverse effects from immunotherapy and did not find significant differences in toxicity between older and younger patients, although arthritis was more common in older patients. Another retrospective study of real-world patients with lung cancer investigated immune checkpoint inhibitor benefits and side effects across ages <60, 60–69, 70–79 and ≥80 years [14]. Interestingly, this study found that the oldest patients (age ≥80) experienced worse survival outcomes than the younger age groups, yet irAEs, steroid use and hospitalizations did not differ by age. Thus, much of the available evidence suggests that PD-(L)1 inhibitors are well tolerated among older adults with cancer, but additional work is needed to definitively determine the benefits of these agents in the geriatric oncology population.

Future perspective

The evidence supporting the use of immunotherapy continues to grow, and so too does the number of older adults who are diagnosed with cancer. As a result, numerous important issues remain to be studied, with some outlined here:

Need for prospective studies focused on older adults with cancer

Much of the current work describing the use of immunotherapy in the geriatric oncology population involves secondary data analyses and retrospective studies. As a result, we lack information about the benefits and risks of immunotherapy for the average older patient seen in routine practice. For example, secondary analyses of randomized trials often lack patients over age 75, and these studies frequently exclude patients with certain comorbid conditions and/or functional impairment. Conversely, although retrospective studies of real-world patients can investigate patients at older ages and those with varying degrees of comorbidity/function, these studies lack a control arm of older patients who did not receive immunotherapy. Thus, these retrospective studies often compare outcomes between older versus younger patients, but we lack data for the counterfactual older adult who did not receive immunotherapy. Ultimately, prospective clinical trials are needed to investigate the impact of immunotherapy specifically focused on the geriatric oncology population.

Need to investigate potential predictors of benefits &/or toxicities associated with immune checkpoint inhibitors

A critical need exists (for both the geriatric oncology population as well as the general cancer population) to identify factors that can predict both response to treatment and potential adverse effects from immunotherapy. For older adults with cancer, potential predictors include geriatric-specific factors (e.g., comorbidity and functional independence), tumor-specific factors (e.g., tumor mutation burden [TMB]), and biomarkers of aging/immune dysregulation. Older adults are not a homogenous population, and thus it is imperative to assess these patients' comorbidity, functional independence, nutrition and psychosocial supports [17]. Importantly, geriatricians have developed tools to help assess and manage older patients' distinct geriatric concerns, but we lack data about whether these tools can predict response/toxicity associated with immunotherapy. Moreover, as patients age so too does the potential for immune dysregulation that may in turn limit the effectiveness of immune checkpoint inhibitors [18]. Importantly, this may be counterbalanced by age-related increases in TMB within some tumor types [19]. TMB has been demonstrated to correlate with activity of immune checkpoint inhibitors across a range of malignancies [20]. Ultimately, additional work is urgently needed to identify factors to predict benefits and/or toxicities associated with immunotherapy, and a particular focus on geriatric-specific issues will be important when evaluating potential predictive factors among older adults with cancer.

Need to study ways to enhance shared decision-making approaches in the geriatric oncology population related to novel cancer treatment

Oncologists often struggle to accurately predict the risks and benefits of novel treatment options. However, a key role of the clinician involves preparing patients and their loved ones for the multitude of different possible outcomes. Notably, patients frequently report overly optimistic perceptions of the potential benefits of treatment, which can complicate their ability to make informed treatment decisions [21]. Additionally, patient-reported outcomes, such as quality of life, symptom burden and illness understanding are largely understudied among patients receiving immune checkpoint inhibitors, and these represent key components of shared decision-making. Moreover, immunotherapy has a wide range of possible serious adverse effects, but also the potential for long-lasting benefits, yet both the risks and benefits are incompletely understood for the geriatric oncology population. Thus, with immune checkpoint inhibitors and their unique toxicity profiles, additional research is needed to understand how best to communicate the possible range of outcomes with patients and their caregivers to enhance shared decision-making.

Conclusion

The geriatric oncology population represents a growing and diverse group of patients that is understudied and often excluded from cancer clinical trials. As the use of immune checkpoint inhibitors continues to increase, and these therapies revolutionize the treatment landscape in oncology, the need for rigorous, high-quality research to understand the risks and benefits of immunotherapies for older adults with cancer will continue to grow. Future efforts to enhance the care delivered to older adults with cancer will require focused attention to the unique needs of the geriatric oncology population and continued investment in research targeting this rapidly growing and often complex population of patients.

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