



Editorial

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Optimal Immunotherapy in Elderly



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Abstract

Management of elderly cancer patients is an increasingly important and complex problem. The use of cytotoxic chemotherapy and new therapies, including immunotherapy in the elderly and very elderly patients (older than 75 years) is limited by under-representation of elderly cancer patients in various types of clinical trials. Oncologists should not immediately lean toward palliative care or non-treatment because of a patient's age. The treatment course should consider the type of cancer, the goals of care, the patient's functional status, and any additional medical conditions.

Keywords: Elderly; Immunotherapy; Gut microbiota; Immune checkpoint inhibitor; Predictive factor

Abbreviations: CGA: Comprehensive Geriatric Assessment; TLR: Toll-like Receptor; irAEs: Immune-related Adverse Events; ICIs: Immune Checkpoint Inhibitors; NSCLC: Non-Small Cell Lung Carcinoma

Introduction

The management of elderly cancer patients is an increasingly important, challenging and complex problem. Cancer occurs predominantly in older individuals. More than 60% of new cancers and more than 70% of cancer deaths occur in patients over the age of 65 years. This age group is growing rapidly therefore the number of cancer patients in this age group will continue to rise [1]. Advanced chronological age alone is not always associated with severe toxicity and poor prognosis [2]. The chronological age alone provides little information regarding an individual's tolerance to cancer treatments. There is considerable heterogeneity among older patients of the same age. Identifying comorbid conditions and geriatric domains health problems that increase the risk of toxicities of anticancer treatment may allow better assessment of the risk/benefit ratio in individual patients [3].

A comprehensive geriatric assessment (CGA) based on validated tools to systematically assess functional, nutritional, cognitive, emotional, and social status as well as comorbidities is recommended by scientific societies. CGA allows detection of multi-domain health problems potentially associated with adverse outcomes and guided decision making about cancer

treatments. Moreover, it can identify older patients with cancer who could benefit from optimal anticancer treatment, those likely to benefit from adapted treatment and allows for supportive care, before and during the anticancer treatment [3].

Chemotherapy is used cautiously in the elderly, because of the high risk of side effects in patients with several criteria of frailty. Immunotherapy constitutes an excellent alternative option in the elderly [3]. Immunotherapy is associated with decreased mortality, longer progression-free survival (PFS), and better tolerability when compared to conventional chemotherapy, for certain types of cancer where immunotherapy is currently considered the first-line agent. This is especially true for certain cancers like metastatic non-small cell lung carcinoma (NSCLC), melanoma, and renal cell carcinoma. Improved clinical outcomes and better tolerability associated with immunotherapy can make it a suitable choice in the elderly with poor response or decreased tolerability to conventional chemotherapy [4].

Organ function decline in the elderly

The bone marrow reserve capacity is reduced because of the decrease in the absolute amount of hematopoietic marrow but the marrow hematopoietic cells generally function well [2].

The immune system

➤ Ageing leads to progressive decline in immune function. This process is known as “immunosenescence” [5]. Naive T cells number decreases due to complete involution of thymus by the age of 50 years while memory T cells number increases because antigen-driven conversion of naive to memory cells continues throughout life [2]. There are differences between males and females in the distribution and cell responses of lymphocyte subsets even inside a population with high prevalence of CMV seropositivity in both sexes. Significant decline in the lymphocytes number with age, is more evident in females, and not in males. Hormonal differences seem to be the most probable cause of this gender-related change in the rate of thymus involution [5].

➤ T cells response to antigens and mitogens decline. Interleukin (IL)-2 production and IL-2 receptors expression decrease in T cells. Production of IL-4, IL-6, IL-10, interferon-gamma, tumor necrosis factor-alpha and transforming growth factor-beta is altered [2]. The monocyte and dendritic cells (DC) functionality after Toll-like receptor (TLR) stimulation were altered. Plasmacytoid DC has reduced capacity to secrete type I IFN in response to TLR or CMV and herpes virus stimulation [3]. T cells dysfunction causes decline in the production and affinity maturation of antibody in response to antigen [2].

The heart: the structural and functional changes of the heart are more pronounced in males than in females. Arrhythmias are common even in asymptomatic elderly. Abnormal electrocardiography (ECG) findings are observed in 57% of the elderly aged ≥65 years, and 80% of them have associated conduction system dysfunction. Paroxysmal atrial tachycardia and ventricular tachycardia were detected in healthy people aged ≥60 years. Serious arrhythmias were uncommon. Exercise induced non-sustained ventricular tachycardia was observed in 3.75% of those aged ≥65 years [2].

Pulmonary function: lung function declines as a result of diminished elastic force of the lung. There is non-uniform alveolar ventilation and decrease in diffusion capacity. The number of alveoli per unit lung volume decreases and the amount of emphysema increases with age even in non-smokers. These changes probably compromise the ability to clear pathogens arriving to the lung through the airways [2].

Renal function: gradual decline in GFR <60 mL/min/1.73m² in a significant proportion of patients [6].

Liver function: liver size and hepatic blood flow decline [6]. The albumin value varies from 20% decrease to almost normal values [6].

Nervous system: axonal degeneration of aged peripheral nerves, secondary demyelination, and subsequent loss of myelinated fibers, are more prominent in thick nerve bundles and their distal part. The conduction velocity of peripheral nerves decreases. A diffuse periventricular white matter change is usually

reported as secondary to microvascular leukoencephalopathy. Most reports show a decline in cerebral blood flow. The function of the blood-brain barrier seems to be affected by age [2].

Does age contraindicate the use of immune checkpoint inhibitors (ICIs)?

A number of studies have demonstrated this issue

ICIs monotherapy: A study from Italy showed that ipilimumab (anti-PD-L1 antibodies) treatment of elderly patients with advanced melanoma in a dose of 3 mg/kg was equally effective and safe in patients aged 70 years or younger. Other published studies have shown that patients with different types of cancer such as NSCLC, clear cell renal cancer, and head and neck cancer between 65 and 75 years of age respond to ICIs as subjects less than 65 years of age. A retrospective study on cancer patients receiving ICIs monotherapy showed no significant difference in overall survival (OS) and PFS between elderly and young patients with multiple metastatic tumors. Most immune-related adverse events (irAEs) that emerged during ICIs treatment were mild or moderate and could be effectively resolved by close clinical observation and appropriate management.

However, a phase 3 registration trials reported irAEs grade 3-5 more frequently in patients over 70 years of age receiving nivolumab (anti-PD-L1) antibodies than in patients less than 65 years of age [7]. ICIs combined with chemotherapeutic agent shave also demonstrated benefit in cancer patients in multiple large studies [7]. The three-drug combination: ICIs combined with anti-angiogenic agents and chemotherapeutic agents in patients with locally advanced or metastatic NSCLC harboring EGFR-sensitive mutations delayed disease progression in both age groups (below 75 years and ≥75 years). The risk remained high in patients ≥75 years group compared with ICIs combined with Bevacizumab [7].

Clinical response to immunotherapy in elderly

Elderly people less than 65 years and those aged between 65 and 75 years, with different types of cancer (NSCLC, clear cell renal cancer, melanoma, head and neck cancer), respond to immunotherapy (anti-PD-1/PDL1, anti-CTLA-4) antibodies in the majority of the studies. This was true for OS, recurrence-free survival, and RECIST response regardless of the location of the cancer. However, some controversies still exist in patients over 75 years of age. There may be a difference in sensitivity to immunotherapy in people over 75 years of age depending on the location of the tumor [3]. Clinical responses have been reported in patients with metastatic melanoma over 90 years of age after treatment with anti-PD-1 or a combination of anti-PD-1 and anti-CTLA-4. This may be explained by an increased ratio of the number of CD8+T cells to regulatory T cells and by the presence of more mutations or neoantigens because of a longer exposure to environmental carcinogens [3]. Combined administration of anti-PDL-1 with conventional treatments (chemotherapy, radiotherapy, etc.) is less preferred in geriatric patients, though they have excellent outcomes in younger patients [4].

The effects of gut microbiota on ICI immunotherapy

Advances have established that gut microbiota can be a promising target to overcome resistance to ICI immunotherapy in elderly patients with lower response rates. Furthermore, some bacterial species have shown to promote improved responses to ICIs. They promote differentiation and function of immunosuppressive immune cells and also inhibit inflammatory cells via gut microbiota derived products such as short chain fatty acids, tryptophan and bile acid metabolites. They also indirectly increase immunogenicity of tumor cells by providing cross-reactivity between antigens expressed in gut microbes and tumor cells to promote the efficacy of ICIs [8].

Predictive factor of response to immunotherapy regimen in elderly patients

There is lack of data about the predictive factor of response to immunotherapy regimen in elderly patients. A previous study showed that a baseline higher lymphocytes/monocytes ratio (LMr) could be a simple efficient tool to predict a higher T cells activity and could be a factor of better response in patients undergoing treatment with ICIs [9].

Immunotherapy toxicity

The toxicities caused by ICIs can affect nearly all organ systems. Most of these toxicities manifest within the first 4 months of treatment, others show up later during the course of treatment. Older adults may have a lower threshold for side effects which warrant closer monitoring while receiving immunotherapy [10]. Moreover, studies suggest that the ability of older patients to recover from the adverse effects of immunotherapy is less compared to the younger population [4]. Different studies have reported a risk of hyperprogression under anti-PD-1/PD-L1 immunotherapy [3]. The incidence of fatal toxicities is observed to occur more frequently in elderly patients compared to younger patients [4].

A retrospective study conducted on 23 patients aged ≥ 75 years showed no statistically significant increase in irAEs as age advances [4]. The incidence of many of these events is fairly similar across all age groups [4]. Furthermore, other studies showed a lack of reported increase in more general or severe (particularly grade 3 or 4) adverse events in both anti-PD-1/ PD-L1 or anti-CTLA-4 monotherapies and in combination therapies of anti-PD-1 and anti-CTLA-4 in elderly patients between 70 and 80 years of age compared to the general population or younger patients [3].

A few studies have reported a slight increase in toxicity with anti-PD-L1 and anti-CTLA-4 combination therapies in people over 80 years of age due to co-morbidity and lack of functional reserve [3]. Patients aged 90 years or older also experienced slightly more side effects and ultimately discontinued immunotherapy earlier than those younger than 90 years [7]. Finally, there is clear

evidence that immunotherapy by blocking the PD-1-PD-L1 axis is less toxic than chemotherapy in the elderly [3].

Real-World ICI effectiveness in older adults

An important limitation factor of the large meta-analysis of PD-L1 inhibitor clinical trials that found comparable efficacy among older and younger adults is that the majority of these trials excluded patients with organ dysfunction or patients with Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2 , which limits the generalizability of their use in more frail older adults routinely cared for in clinical practice [11].

Conclusion

The risk versus benefit ratio must be well evaluated before initiating management for each elderly patient as there are significant variations in health status across individuals. Hence, the intensity of cancer therapy has to be suited for each patient in the geriatric category.

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