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Impact of Immunosenescence on Immune-Related Adverse Events in Elderly Patients With Cancer

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ABSTRACT

Immune checkpoint inhibitors (ICI), have transformed the management of several types of cancers; however, immune-related adverse events (irAEs) may cause treatment interruptions, chronic toxic effects, and death. Elderly patients are at high risk of cancer. Compared with traditional chemotherapy, immunotherapy has become a better alternative choice for elderly patients with cancer due to its high efficiency and low toxicity. However, the emergence of immunosenescence accompanied by advancing age raises safety concerns for ICI. Therefore, we summarize the characteristics of irAEs occurred in elderly patients with cancer and the physiological characteristics of immunosenescence, which will lay a theoretical foundation for the safety management of immunotherapy in elderly patients with cancer.

Although immune checkpoint inhibitors (ICI), represented by programmed cell death 1 (PD-1)/programmed cell death-ligand 1 (PD-L1) inhibitors, have revolutionized the treatment of various cancers, immune-related adverse events (irAEs) have increased the complexity of ICI therapy. Some Grade 2 and most Grade 3 or higher irAEs can lead to treatment interruption, hormone therapy, or even life-threatening situations. Therefore, irAEs are considered a major obstacle to tumor immunotherapy based on ICI. Cancer is often considered an "age-related disease," as the incidence of cancer in the population tends to increase with age. However, with advancing age, the immune system of elderly patients exhibits characteristics such as decreased ability to fight pathogens and sustained inflammatory responses, collectively referred to as "immunosenescence." The impact of immunosenescence on the safety and efficacy of ICI therapy is a major focus of current clinical research.

An early retrospective study compared the incidence of irAEs in patients aged ≥70 and <70 participating in Phase I trials of ICI and indicated a significantly higher incidence of grade 1–2 irAEs in patients aged ≥70 compared to those aged <70 ($p<0.001$). However, there was no statistically significant difference in the incidence of grade 3–4 irAEs between the two groups (22% vs. 13%, $p=0.12$) [1]. Subsequently, a larger prospective study including 603 patients with solid tumors receiving ICI monotherapy, showed a significantly higher incidence of grade 2 or higher irAEs in patients aged ≥70 compared to those aged <70 (33% vs. 25%, $p=0.035$) [2]. In the recent ELDERS study, a prospective cohort study evaluated the safety of PD-1/PD-L1 inhibitors in elderly patients. The study revealed a higher incidence of grade 3–5 irAEs in patients aged ≥70 compared to those aged <70, but it did not reach statistical significance (18.6% vs. 12.9%, $p=0.353$) [3]. For cancer patients aged ≥75, a summary safety analysis of the KEYNOTE-010/024/042 clinical trials showed that in 264 non-small cell lung cancer patients aged ≥75, the incidence of any-grade irAEs and grade 3–5 irAEs was similar to that in patients aged <75 (any irAEs: 24.8% vs. 25.0%; grade 3–5 irAEs: 9.4% vs. 7.1%) [4]. Another retrospective case–control study compared the incidence of any-grade irAEs and grade 3–5 irAEs among patients with multiple cancer types aged <65, 65–74, and

≥75, and showed no statistically significant differences (any irAEs: 60% vs. 63% vs. 56.9%, $p > 0.05$; grade 3–5 irAEs: 18.9% vs. 16.2% vs. 11.0%, $p > 0.05$) [5]. Due to strict inclusion criteria in clinical trials, there is a severe lack of treatment data for cancer patients aged 80 and above. A recent multicenter international retrospective study conducted by Nebhan et al. provided preliminary insights into the safety of ICI monotherapy in 928 cancer patients aged 80 and above. The results showed that a total of 383 patients (41.3%) experienced irAEs, with 113 cases (12.2%) experiencing Grade 3–5 irAEs, and a treatment discontinuation rate of 16.1% due to irAEs. After further age grouping, there was no significant difference in the incidence of irAEs among patients aged <85, 85–90, and ≥90 [6]. However, it is worth noting that patients aged 90 and above had a discontinuation rate due to irAEs more than twice as high as that of patients aged 80–90 (30.9% vs. 15.1%, $p = 0.008$). Together, the conclusions regarding the incidence of irAEs in elderly patients with cancer compared to younger patients are inconsistent, which may be related to the classification of irAE severity, age grouping, cancer types, etc. However, many studies have suggested a higher incidence of irAEs in elderly patients compared to younger patients, highlighting the need to strengthen monitoring and management of immune-related toxicities in elderly patients with cancer. The clinical trials of irAEs occurred in elderly and younger adults with cancers are listed in the summary table (Table 1).

Statistics indicate that irAEs encompass more than 70 different types, affecting nearly every organ, including the skin, colon, lungs, kidneys, heart, nervous system, and endocrine system, among others. Recent research has found different patterns of irAEs between elderly patient and younger patients. A higher incidence of checkpoint inhibitor pneumonitis (CIP) is reported to range from 12% to 19% in elderly patients, well above the general population [10, 11]. Chronic lung diseases such as lung interstitial changes or thoracic radiation are considered as key factors of CIP [12, 13]. Therefore, the higher prevalence of chronic lung diseases in elderly patients may contribute to the higher incidence of CIP in this population. In addition, numerous studies showed that immune-related skin toxicity was also positively associated with age (OR = 1.04; 95% CI: 1.01–1.06, $p = 0.04$), while younger age was negatively correlated (OR = 0.36, 95% CI: 0.14–0.75, $p = 0.006$) [14, 15]. In contrast, the incidence of immune-related hypothyroidism was lower in the elderly group compared to the younger group [2, 5]. However, due to the low frequency of other irAEs such as hepatitis, myocarditis, colitis, and hypophysitis, they have not been adequately compared between elderly and younger patients. Subsequent studies with large sample population are needed to explore the characteristics of irAEs in elderly patients with cancer, which is important for ICI treatment decision-making and irAEs toxicity management in the elderly.

Considering the limitations of assessing physiological function in elderly patients based solely on chronological age, a comprehensive geriatric assessment (CGA) conducted by geriatricians evaluates elderly patients across various aspects such as physiological status, comorbidities, cognitive function, nutritional status, psychological well-being, social support, and concurrent medication usage. This assessment categorizes elderly patients into different functional groups to predict treatment toxicity and survival outcomes. The Geriatric-8 (G-8) is a comprehensive assessment scale designed to evaluate the degree of frailty in patients aged 70 and above. Recent studies showed that higher G-8 score indicated increased irAE-related hospitalization rate (54% vs. 29%; $p = 0.02$), prolonged hospitalization duration (8 vs. 5 days, $p = 0.06$), and increased rates of immunosuppressive drug use and treatment termination (58% vs. 36%, $p = 0.06$) [16]. CGA holds predictive value for the safety of elderly patients with cancer after receiving ICI treatment, but validation with large sample is still required. In addition, further exploration of assessment tools for predicting the risk of irAEs in elderly patients is warranted.

The exact mechanism by which immunosenescence may contribute to irAEs is unclear several possibilities need to be considered. The aging T cells have high differentiation ability and low proliferation ability, exhibiting both specific high cytotoxicity and non-specific secretion of inflammatory factors, leading to the occurrence of irAEs. CD45RA + CCR7-CD27-CD28-CD57 + KLRG-1+ is considered the phenotype of aging T cells, also known as T effector memory re-expressing CD45RA (TEMRA). A recent study revealed an increase in CD8 + TEMRA cells in the peripheral blood of patients treated with anti-PD-1 inhibitors, as well as in the peripheral blood and heart tissue of PD-1 knockout mice [17]. This suggests that the accumulation of TEMRA cells caused by aging may be an important cause of immune-related adverse reactions in elderly patients with cancer. The senescence-associated secretory phenotype (SASP) is an important part of aging, which promotes the transmission of damage signals from senescent cells to neighboring cells in a non-autonomous manner. SASP includes immune regulatory factors such as IL-1β, IL-6, IL-8, and CXCL10; growth factors such as HGF, VEGF, and FGF; and matrix metalloproteinases. Recent data suggested substantial overlap between SASP and predictive biomarkers for irAEs, indicating that the senescence-induced immune microenvironment may contribute to the development of irAEs, and the senescence of T lymphocytes is the main cause of SASP formation and the senescence microenvironment. Future research needs to explore the role of SASP and the senescence of T lymphocytes in irAEs based on elderly patients or elderly animal models, and the combination analysis can better reveal the effect of immunosenescence in the development of irAEs.

In clinical practice, although current studies yield inconsistent conclusions regarding the comparison of irAEs in elderly versus younger cancer patients, there is still a higher frequency of mild to moderate irAEs in elderly patients, accompanied by a unique pattern of irAEs. This suggests the need to strengthen and emphasize the management of irAEs in elderly patients with cancer. Furthermore, immunosenescence refers to the decline in immune function within the body, and the use of chronological age cannot accurately define the true 'elderly' population. Therefore, it is imperative to establish a multidimensional risk assessment system that combines immunosenescence characteristics aiming to assess the risk for elderly patients with cancer receiving ICI treatment. The functionality and adaptability of the immune system are pivotal factors ensuring the safety and efficacy of cancer immunotherapy. According to the characteristics of immunosenescence, the evolving process of immunosenescence with advancing age may render elderly patients with cancer more susceptible to irAEs. However, the current understanding of the molecular mechanisms associated with

TABLE 1 | Clinical trials of irAEs occurred in elderly and younger adults with cancers.

Year of publication	Clinical trial or first author	Research type	Number of samples	Cancer type	Incidence of irAEs
Age ≥ 70 years vs. < 70 years					
2016	Singh et al. [7]	Meta analysis	$n = 212/818$	Renal cell carcinoma; Melanoma; NSCLC	G3-5 irAEs:71.7% vs. 59.4%
2018	Herin et al. [1]	Retrospective study	$n = 47/147$	Solid tumor	G1-2 irAEs: higher incidence in patients aged ≥ 70 years, $p < 0.05$ G3-4 irAEs:22% vs. 13%, $p = 0.12$
2020	Baldini et al. [2]	Prospective study	$n = 191/412$	Melanoma; NSCLC; Urothelial carcinoma; Renal cell carcinoma	G1-2 irAEs:33% vs. 25%, $p = 0.035$
2021	Gomes et al. [3]	Prospective study	$n = 70/70$	NSCLC; Melanoma	G3-5 irAEs:18.6% vs. 12.9%, $p = 0.353$
Age ≥ 75 years vs. < 75 years					
2019	Nosaki et al. [4]	Meta analysis	$n = 264/NA$	NSCLC	Any grade of irAEs:24.8% vs. 25.0% G3-5 irAEs:9.4% vs. 7.1%
2020	Samani et al. [5]	Retrospective study	Age < 65 years/65–74 years/≥ 75 years: $n = 185/154/109$	Melanoma; Renal cell carcinoma; NSCLC	Any grade of irAEs:60% vs. 63% vs. 56.9%, $p > 0.05$; G3-5 irAEs:18.9% vs. 16.2% vs. 11.0%, $p > 0.05$
2020	Ksienski et al. [8]	Retrospective study	Age < 65 years/65–74 years/≥ 75 years: $n = 214/214/99$	NSCLC	Any grade of irAEs:28.6% vs. 27.8% vs. 27.4%, $p > 0.05$
2021	Morimoto et al. [9]	Retrospective study	$n = 86/117$	NSCLC	G3-5 Interstitial pneumonia: 16.0% vs. 2.1%, $p = 0.02$
Age ≥ 80 years					
2021	Nebhan et al. [6]	Retrospective study	$n = 928$	NSCLC; Melanoma; Urothelial carcinoma	Any grade of irAEs:41.3% G3-5 irAEs:12.2%

immunosenescence is limited, lacking gold standard markers for aging and animal models suitable for irAEs studies. These gaps represent areas for further exploration in the field of cancer immunotherapy research.

Author Contributions

Acquisition and analysis of data: Jiayi Gao. Interpretation of data: All authors. Drafting of the manuscript: Jiayi Gao. Critical revision of the manuscript for important intellectual content: Lin Li. Administrative, technical, or material support: Yue Yuan, Liuer He. Study Supervision: Lin Li.

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Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

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