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Immune checkpoint inhibition in the context of aging

Constantin N. Baxevanis[1,2,*], Ourania E. Tsitsilonis[2]

[1]Cancer Immunology and Immunotherapy Center, Saint Savas Cancer Hospital, Athens 11522, Greece.
[2]Flow Cytometry Unit, Section of Animal and Human Physiology, Department of Biology, National and Kapodistrian University of Athens, Athens 15784, Greece.

***Correspondence to:** Constantin N. Baxevanis, Cancer Immunology and Immunotherapy Center, Saint Savas Cancer Hospital, Athens 11522, Greece. E-mail: cnbaxevanis@biol.uoa.gr

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Abstract

Advancing age substantially increases cancer risk, primarily due to progressive biological alterations over time. With the global population aging rapidly, the incidence of cancer is also rising. In cancer immunotherapy, patient age is emerging as a critical determinant for both identifying and predicting responses to immune checkpoint inhibitors. Aging is accompanied by significant changes in the immune system, notably a decline in T-cell function and a reduction in tumor-infiltrating lymphocytes, which collectively reshape the tumor microenvironment and weaken antitumor immunity. Immune senescence compromises the ability to recruit and maintain functional TIL activity, thereby limiting the benefits of immune checkpoint inhibitors therapy. Furthermore, senescent tumor cells influence their surroundings by releasing a broad spectrum of pro-inflammatory cytokines and chemokines, a phenomenon termed the senescence-associated secretory phenotype, while simultaneously upregulating immune inhibitory markers such as PD-L1. In addition, age-related immune dysregulation exacerbates cellular exhaustion, leading to abnormal expression of key biomarkers that govern immune checkpoint inhibitors efficacy and ultimately attenuating antitumor immune responses. This perspective discusses the mechanisms through which aging alters systemic immunity and the tumor microenvironment, thereby reducing immunotherapy effectiveness. By integrating current mechanistic insights into the interplay between aging and cancer immunobiology, we highlight potential aging-related biomarkers that may improve therapeutic strategies in geriatric oncology. A deeper understanding of these interactions is essential for developing personalized immunotherapeutic approaches tailored to the unique needs of elderly cancer patients.

Keywords: Cancer, aging, immune checkpoint inhibitors, older cancer patients, cancer immunotherapy

1. Introduction

Over the past two decades, our understanding of immune checkpoints has expanded considerably. These regulatory molecules, expressed on T cells and their corresponding ligands on tumor and other cell types, suppress T-cell activity and enable tumors to evade immune surveillance. To counteract this inhibition, a novel class of therapeutic agents, known as immune checkpoint inhibitors (ICIs), was developed to disrupt these suppressive pathways and restore the immune system's ability to recognize and eliminate cancer cells. The transformative clinical impact of this strategy was recognized with the 2018 Nobel Prize in Physiology or Medicine, awarded to Dr. James Allison and Dr. Tasuku Honjo for their groundbreaking work on targeting immune checkpoints.

Despite the transformative advances immunotherapy has introduced to cancer treatment, its effectiveness in older patients remains insufficiently investigated. As cancer incidence continues to rise among the elderly, it is essential to understand how age-related alterations, particularly those affecting T-cell function, influence the clinical outcomes of ICIs. Aging is characterized by complex changes within the immune system, including a decline in T-cell activity and a reduction in tumor-infiltrating lymphocytes (TILs). This process of immunosenescence not only compromises the body's intrinsic antitumor defenses but also reshapes the tumor microenvironment, potentially reducing the therapeutic benefits of ICIs. Moreover, evidence suggests that the accumulation of senescent cells with age, including those expressing inhibitory molecules such as PD-L1, may further complicate interactions between tumors and immune cells. Although immune cells are generally capable of eliminating senescent cells, some persist and evade detection through mechanisms that remain poorly understood. Elucidating these changes within the immune-tumor microenvironment is crucial for refining cancer immunotherapy strategies, particularly through the identification of aging-related biomarkers that can predict ICI response and guide treatment optimization.

Recent studies have emphasized the impact of immune dysregulation, characterized by T-cell exhaustion and disrupted cytokine signaling, on therapeutic outcomes. Preclinical research has shown promise for strategies designed to counteract immunosenescence, including the use of senolytic or senostatic agents. In parallel, targeting key signaling pathways such as mitogen-activated protein kinases (MAPK) and p38 has not only restored T-cell functionality but also enhanced the cytotoxic activity of immune cells against tumors. Combining these approaches with ICIs may help overcome challenges associated with the aging immune system. Moreover, age-related immune system reorganization in both humans and animal models induces a persistent, low-grade inflammatory state known as the senescence-associated secretory phenotype (SASP)[1-3]. Substantial evidence indicates that this immune remodeling compromises tumor immunosurveillance, thereby increasing cancer risk and diminishing the effectiveness of anticancer vaccines and ICIs. Compelling data also suggest that activation of immunosuppressive pathways, particularly those involving myeloid cells and regulatory T cells (Tregs), plays a critical role in tumor progression and reduces ICI efficacy[4-8]. Collectively, these immunosuppressive processes exacerbate age-related immune decline, contributing to the variable therapeutic responses observed in elderly patients. As the immune system shifts with age, its ability to detect and eliminate tumors weakens, rendering immunotherapies less effective and more likely to induce adverse effects in older individuals. These combined challenges, which often result in poorer clinical outcomes, underscore the need for clinical trials specifically designed to examine how aging influences immune function and treatment tolerability[9,10]. A deeper understanding of age-related changes in immune checkpoint regulation could enable the development of personalized immunotherapies that are both effective and safe for elderly patients. As cancer therapies continue to evolve, strategies to address the unique challenges posed by aging must advance in parallel. By integrating mechanistic insights with clinical progress, researchers can design targeted immunotherapeutic approaches tailored to the distinct immune profiles of older individuals, ultimately improving treatment outcomes and advancing our understanding of the interplay between aging and cancer immunology.

2. Aging and Immune Suppression

Aging induces multiple alterations in T-cell functionality, making the study of T-cell aging particularly complex. As individuals grow older, a range of modifications occur within the T-cell compartment that collectively reduce immune efficiency[11,12]. Research consistently demonstrates that aging affects various T-cell subsets, including helper, cytotoxic, and regulatory populations, all of which are essential for mounting an effective immune response. These changes manifest as a reduced capacity to express activation markers on the cell surface, diminished cytokine secretion, and a lower proliferative rate[3,4,9,10]. For example, T cells from young mice exhibit a robust increase in PD-1 expression following stimulation, whereas this response is largely absent in aged mice, suggesting that older T cells fail to upregulate PD-1 effectively upon activation. Interestingly, although stimulation does not significantly elevate PD-1 expression on aged T cells, other activation markers such as CD25 and CD69 still show increased expression[13-16].

These findings suggest that the immune system of older individuals may not respond as effectively to immunotherapeutic interventions. Indeed, multiple studies have documented reduced immunotherapy efficacy in elderly patients[17-20]. The natural decline in immune function caused by immunosenescence presents a major barrier to the success of these treatments, particularly in cancer therapy[18,19]. Because both aging and tumor progression contribute to heightened immunosuppression and promote immunosenescence, researchers have developed strategies to counteract the suppressive effects of myeloid-derived suppressor cells (MDSCs) and Tregs[20,21]. MDSCs are well recognized as key mediators of resistance to ICI therapy[9]. Moreover, combining ICIs with pharmacological agents that inhibit MDSC function has been shown to improve clinical outcomes[22-25]. Similarly, targeting specific surface molecules on Tregs has emerged as a promising approach to enhance the efficacy of cancer immunotherapy[21]. Notably, concurrent depletion of both MDSCs and Tregs produced markedly improved therapeutic responses in aged mice bearing B16 melanoma tumors[26]. These observations highlight the profound challenge posed by an immunosuppressive tumor microenvironment in elderly patients. Addressing age-related immune dysfunction could augment the activity of tumor-reactive T cells and lead to better clinical outcomes. To achieve optimal results, treatment strategies must be tailored to correct immune deficits arising from both aging and tumor progression. A deeper understanding of how aging shapes tumor-associated immune deficiencies will be essential for designing more effective immunotherapies for elderly patients, who represent one of the highest-risk populations for cancer.

3. The Role of Senescence in Antitumor Immunity and Immune Checkpoint Inhibition

Progressive alterations in immune function, characteristic of immunosenescence, reflect an inevitable and complex transformation associated with aging. This evolution has raised important questions regarding the relationship between immune aging and tumor development, leaving uncertain whether cellular senescence and its associated secretory phenotype (SASP) ultimately facilitate or hinder antitumor immunity. Emerging evidence suggests that the SASP can promote immune cell activation and enhance their infiltration into tumors by improving antigen presentation and strengthening antitumor responses through the activation of type I/II interferon (IFN) pathways[27-29]. For example, in a liver cancer model, senescence was linked to intrinsic changes in gene transcription and protein expression that increased responsiveness to IFNγ. Senescent cells exposed to IFNγ, both in vitro and in vivo, exhibited stronger activation of IFNγ-related effectors compared with non-senescent cells. Furthermore, an intact IFNγ signaling pathway and the presence of environmental IFNγ were essential for effective $CD8^+$ T cell-mediated clearance of senescent tumor cells. In this

context, IFNγ also enhanced the surface expression of major histocompatibility complex class I (MHC-I) molecules in both proliferating and senescent cells, with senescent cells showing a particularly pronounced increase. This was accompanied by elevated levels of antigen-processing transporters, other antigen-processing proteins, and key components of the MHC-I complex[27]. Such heightened sensitivity to IFNγ, resulting in increased MHC-I expression, suggests that senescence may improve antigen presentation in non-immune cells and thereby strengthen tumor immunosurveillance. Notably, blocking IFNγ signaling did not affect the onset of senescence or the SASP but did impede tumor regression, indicating that both the tumor microenvironment and SASP components cooperate to shape senescence-driven immune surveillance.

Similarly, Marin *et al.* demonstrated that senescent cancer cells exhibit an enhanced interferon (IFN)-driven transcriptome profile along with increased expression of molecules involved in MHC-I antigen presentation. Their study further showed that dendritic cells co-cultured with ovalbumin (OVA)-expressing senescent tumor cells were significantly more effective at activating OVA-specific $CD8^+$ T cells than those co-cultured with non-senescent cells[28]. These findings indicate that senescent cells possess notable adjuvant properties, supporting both the recruitment and activation of dendritic cells as well as efficient antigen delivery. In a therapeutic tumor model, immunization of B16.F10 melanoma-bearing mice with syngeneic senescent tumor cells resulted in a marked delay in melanoma progression, which correlated with increased tumor infiltration of highly activated $CD8^+$ T cells[28]. Comparable results were observed in human studies, where TILs co-cultured with autologous senescent cancer cells showed stronger antigen-dependent activation of $CD8^+$ T cells compared to cultures with non-senescent cancer cells[28].

Research on senescent tumors and immunotherapy has yielded promising yet complex results. Several studies have shown that the SASP can enhance antitumor responses when combined with ICIs, such as anti-PD-1 and anti-PD-L1, although the therapeutic benefits depend heavily on the specific treatment protocols employed. For instance, Hao *et al.* demonstrated that transferring senescent ovarian cancer cells induced by cisplatin and expanded using a topoisomerase I inhibitor sensitized tumors to anti-PD-1 therapy, ultimately prolonging survival in a syngeneic murine tumor model[30]. Another study revealed that regulating SASP activity via the cyclic GMP-AMP synthase/stimulator of interferon genes pathway promoted immune cell recruitment and improved the response of homologous recombination deficient tumors to checkpoint blockade[29]. This work not only suggested that a predisposition to cellular senescence may predict treatment success but also identified a distinct SASP profile that increased tumor susceptibility to combined immunotherapeutic strategies. Additionally, Shahbandi *et al.* reported that sequential treatment of mammary tumors, with initial chemotherapy followed by PD-L1 and CD80 targeting, significantly enhanced T cell infiltration and therapeutic outcomes[31]. However, the variability observed with single-agent treatments suggests that the concurrent expression of immunosuppressive proteins may contribute to resistance against checkpoint inhibition. Similarly, combining anti-CTLA-4 with anti-PD-1 produced a markedly stronger effect than either antibody alone, with nearly 40% of tumors exhibiting a relapse delay exceeding one month, a result not seen with monotherapy[31]. Despite these advances, complete tumor eradication and cures remain elusive, highlighting the need for further research to unravel the multiple immune suppression pathways activated during senescence.

Among the genes upregulated during therapy-induced senescence, many are involved in antigen presentation[31]. However, these senescent tumors often do not show a corresponding increase in immune cell infiltration. This discrepancy may result from reduced recruitment of lymphocytes into the tumor microenvironment or the activation of suppressive mechanisms that limit lymphocyte proliferation[31,32]. Variations in the type and concentration of factors released as part of the SASP may influence the density, diversity, and function of immune cells within the tumor. In addition to the increased expression of antigen-presentation genes, therapy-induced senescent tumors also exhibit significant upregulation of several immunosuppressive genes with potentially overlapping functions[31]. For example, studies of chemotherapy-treated tumor cells have reported expression of the immunoregulatory protein CD80 along with co-expression of PD-L1 and galectin-9 on distinct subsets of senescent cells. The detection of CD80 on senescent cells is a novel finding, while the upregulation of PD-L1 is consistent with previous observations in both chemotherapy-induced and replicative exhaustion models[33,34]. Moreover, variability in PD-L1 expression among senescent cells has also been documented[33]. Although all senescent tumor cells share a general SASP profile, those positive for CD80 are primarily linked to NF-κB signaling pathways, whereas cells expressing PD-L1 together with galectin-9 are more closely associated with IFN-related gene networks.

Cellular senescence may influence not only the likelihood but also the anatomical sites, onset, and persistence of immune-related adverse events (irAEs) following ICI therapy. While some clinical data suggest that older patients have a higher overall risk of irAEs, particularly cutaneous toxicities[35,36], the evidence remains inconsistent. Senescent cells contribute to a pro-inflammatory environment through the SASP, releasing IL-6, IL-8, and IFN-γ[37,38]. Notably, recent trials show that IL-6 blockade can both prevent and mitigate irAEs[39,40], whereas other studies paradoxically associate lower baseline IL-6 levels with more frequent and severe toxicities[41]. Additionally, elevated PD-L1 expression within senescent cells, whether in the tumor microenvironment or the surrounding stromal compartments, may underlie age-related differences in irAE development[34]. Interestingly, ICIs themselves appear capable of eliminating senescent cells in some contexts, as shown by studies reporting a reduction in senescent cell burden following checkpoint blockade[33].

Overall, these findings indicate that distinct downstream signaling pathways regulate SASP gene expression, raising new questions about tumor heterogeneity and its impact on both the senescence process and the antitumor immune response. Moreover, aging and cellular senescence appear to influence how tumors, their microenvironments, and the broader immune system respond to checkpoint blockade, as well as the range of associated toxicities. Although clinical data on age-related differences in ICI outcomes remain inconclusive, animal and in vitro studies emphasize a key role for senescent cells in determining both therapeutic efficacy and the risk of irAEs. To fully understand these interactions and to guide strategies combining ICIs with senolytic or senescence-modulating agents, dedicated mechanistic studies and prospective clinical trials focused on senescent cell clearance are urgently needed.

4. Biomarkers for Immune Checkpoint Blockade in the Elderly

Aging plays a crucial role in both cancer development and prognosis[42]. Biological markers of aging not only assist in diagnosis but also provide insights into potential treatments for age-related diseases such as cancer[43]. Preclinical studies mainly involve experimental investigations in animal models, such as mice, to evaluate the biological effects, mechanisms, and potential efficacy or toxicity profiles of ICIs. These studies have significantly advanced understanding of how aging affects immune responses and ICI efficacy. In elderly mice, preclinical data consistently demonstrate immunosenescence, a decline in immune function characterized by reduced naïve T-cell populations, altered cytokine production, and a less responsive tumor-infiltrating lymphocyte (TIL) environment[44-46]. These changes can influence the effectiveness of ICIs, which depend on reinvigorating T-cell activity. Monotherapies have shown reduced effectiveness in a mouse model of triple-negative breast cancer[44], and combined regimens underperformed in the B16 melanoma model[46], whereas other studies report that PD-1 blockade is more effective in aged mice[47]. Additionally, differences in ICI treatment efficacy between older and young animals have been reported. In an orthotopic, transplantable B16 melanoma model, young tumor-bearing mice responded robustly to anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapies. In contrast, aged mice showed no tumor control with anti-PD-L1 alone, only modest benefits from anti-CTLA-4, while anti-PD-1 retained similar efficacy to that observed in young mice[46]. The authors suggested that the preserved anti-PD-1 activity in older animals may result from elevated baseline and tumor-induced PD-1 expression on T cells[48]. Further investigation of this observation could provide valuable insights into how aging influences the PD-L1/PD-1 axis in cancer immunotherapy.

In many cancers, aging is associated with genetic alterations such as mutations, altered DNA repair patterns, and copy number variations[49-55]. Cells that become senescent due to DNA damage show variable PD-L1 expression, with older individuals accumulating more PD-L1–positive senescent cells[33,56,57]. This fluctuation in PD-L1 plays a key role in both the formation of senescent cells and the inflammation linked to aging, suggesting that targeting these PD-L1–positive cells with ICIs might represent a novel anti-aging therapeutic strategy[33,56]. Moreover, tumors across different age groups exhibit distinct responses to ICIs, likely due to differential expression of immune genes related to aging. This pattern parallels the increased cancer incidence and mortality observed in older populations[49]. One possible explanation is that age-related changes in the immune system alter both the number and functionality of lymphocytes within tumors, which are essential for eliminating cancer cells. Consequently, the lower abundance of these immune cells in elderly patients, attributed to immunosenescence, may reduce immunotherapy effectiveness. Additionally, dysregulation of the aging immune system might lead to enhanced immune cell exhaustion, as reflected by abnormal patterns in key biomarkers involved in checkpoint inhibition, ultimately weakening therapeutic responses. Encouragingly, current data do not consistently show that older patients experience poorer responses or more severe side effects during ICI therapy. Several meta-analyses have evaluated the benefits of ICIs in older versus younger patients. One pooled analysis of anti-PD-1/PD-L1 trials stratified participants into those aged 75 and above and those under 75 years, finding that patients aged 75 and older derived no significant progression-free survival (PFS) or overall survival (OS) advantage from these agents[58]. Another meta-analysis applied age cut-offs of 65 and 75 years to compare outcomes with anti-PD-1/PD-L1 and anti-CTLA-4 therapies[59]. It also reported no meaningful differences in PFS or OS between patients above or below 65 years. Consistent with these findings, Kim *et al.*[60] observed no age-related disparities in PFS or OS, although patients under 75 showed a statistically significant OS improvement and a nonsignificant trend toward longer PFS. Another meta-analysis focusing on advanced non-small cell lung cancer demonstrated that ICIs significantly improved both OS and PFS compared with chemotherapy in elderly patients, particularly those aged 65 to 74[61]. These survival benefits were largely consistent across subgroups defined by race, tumor histology, ICI agent, treatment regimen, and line of therapy. However, certain factors, including age 75 and above, Eastern Cooperative Oncology Group (ECOG) performance status of 2 or higher, and PD-L1 expression below 1%, appeared to reduce ICI efficacy, although confirmation in large randomized trials is needed. In a melanoma study[62], 26 patients over 75 years old (median age 77) were matched with 34 younger individuals (median age 57). Baseline characteristics were comparable between the two groups. Median PFS did not differ significantly (5.5 months in the older group versus 7.5 months in the younger group). Tolerability was similar: 35% of patients aged 75 and above and 28% of those under 75 completed four treatment cycles. Rates of grade 2 to 4 immune-related adverse events were 58% and 66%, respectively, while hospitalizations for grade 3 to 4 toxicities occurred in 63% of elderly patients and 69% of younger patients. When further subdivided into groups aged over 80 and 75 to 79 years versus 65 to 74 and under 65 years, no differences were found in response rates or grade 3 to 4 toxicity.

It is important to note that in this study[62], the response rate was higher in the younger patient group compared to the older group

(56% *vs.* 38%, respectively), although this difference was not statistically significant, possibly due to the relatively small number of patients in each group. The variation in response rate may be attributed to differences in melanoma subtypes between the two groups. Notably, a relatively high proportion of older patients (30%) had either mucosal or uveal melanoma, both known to have lower response rates compared to cutaneous melanoma[63-65], which was 2.5 times higher than that observed in the younger group (12%). Conversely, the percentage of cutaneous melanoma was higher among younger patients than older ones (75% *vs.* 51%, respectively). These differences became more pronounced when examining the cutaneous melanoma subgroup, which showed a significantly higher response rate in younger patients (67% *vs.* 29%). Interestingly, among non-cutaneous melanoma patients, elderly patients showed a 50% response rate compared to 25% in the younger group, although this difference was not statistically significant due to the limited sample sizes. Therefore, beyond the factors discussed above, the differing histological melanoma subtypes may affect the ability to draw definitive conclusions when comparing response rates between these age groups.

To improve outcomes with immune checkpoint blockade, researchers are investigating the mechanisms underlying patient responses, with multiple studies highlighting the central role of immunosenescence[66-69]. Understanding the molecular mechanisms related to immunosenescence is essential for discovering biomarkers that could serve as potential therapeutic targets. Although the field is still in its infancy, data suggest synergy between anti-aging treatments and checkpoint immunotherapy[70-72]. One promising approach to address this challenge involves combining immunotherapy with agents that either reprogram senescent cells or eliminate them, known as senolytic therapies[73-77]. Given that the MAPK pathway is critical for secreting numerous bioactive molecules, including proinflammatory cytokines and chemokines that make up the SASP, and that sestrins promote aging in T cells by activating MAPK, targeting components within the sestrin-MAPK complex could potentially modulate the detrimental changes in T cell function associated with senescence[3,72,78]. However, prolonged suppression of sestrins may allow DNA-damaged senescent cells to accumulate, potentially increasing cancer risk, which is why a short-term inhibition strategy may be preferable for immunotherapeutic treatments[79]. Efforts to target the MAPK pathway using BRAF and MEK inhibitors have shown mixed results. Recent preclinical and clinical studies combining these inhibitors with anti-PD-1/PD-L1 therapy reported improved antitumor responses and better tolerability. In particular, MEK inhibition has been linked to expansion of effector T cells, while reducing exhaustion and apoptosis[80-84]. In a systematic study, Gurusamy *et al.* found that inhibiting Mapk14, the gene encoding p38 kinase, significantly enhanced T cell proliferation and memory formation, while reducing oxidative and genomic stress[85]. Other studies demonstrated that p38 inhibition can reverse DNA damage and ameliorate senescence-related dysfunction in primary human T cells, independently of PD-1 pathways[79,86]. Notably, while earlier research focused on suppressing p38 activity in already senescent T cells, Gurusamy *et al.* emphasized the importance of blocking p38 during the initial activation and expansion of less differentiated T cells[85]. Their findings suggest that p38 inhibition is crucial during the generation of tumor-reactive, gene-engineered T cells, enhancing their differentiation and cytotoxic efficiency, and raise the possibility of combining chimeric antigen receptor T cells, PD-1 inhibitors, and p38 blockers as an effective treatment in certain cancer contexts. Additionally, evidence indicates that TLR8 signaling can prevent or reverse T cell senescence induced by Tregs and tumors[87-89]. Since the development of an immunosuppressive tumor microenvironment is a major barrier to successful immunotherapy, targeting TLR8 could represent another strategy to enhance T cell function alongside immune checkpoint blockade. Despite progress in this field, it remains essential to deepen our understanding of how immunosenescence drives age-associated tumor development and to develop novel in vivo aging models that more accurately reveal the mechanisms behind immune suppression, thereby uncovering new strategies for anti-aging immunity and cancer therapy.

5. Multifactorial Barriers to Optimal ICI Use in the Elderly

Beyond the need for geriatric assessment-driven personalization, several systemic issues limit the safe and effective use of ICIs in older patients. First, age-related physiological changes and comorbidities can exacerbate immune-related toxicities. Older adults are more susceptible to steroid-induced complications, such as hyperglycemia and delirium, when managing irAEs and often require tailored monitoring and dose adjustments[90]. Second, the vast majority of pivotal phase III ICI registration trials employ strict eligibility criteria; for example, 98% exclude patients with an ECOG performance status greater than 1, and most disallow significant comorbidities. This results in underrepresentation of patients aged 75 years and older and limits the generalizability of observed efficacy and safety profiles[91]. Third, this evidence gap has produced few geriatric-specific guidelines. While the American Society of Clinical Oncology and the European Society for Medical Oncology provide broad irAE management algorithms, there is limited high-level guidance on adapting these protocols for frail elderly patients or those with polypharmacy[92]. Addressing these interconnected challenges will require not only personalized dosing strategies but also regulatory mandates for inclusive trial design, dedicated toxicity-management studies, and the development of geriatric oncology recommendations specific to ICIs.

6. Conclusions and Future Perspectives

Recent evidence suggests that immunotherapy may offer a viable treatment option for elderly patients whose conditions have proven resistant to conventional therapies. This emerging data highlights the urgent need to identify new molecular targets that can enhance the effectiveness of immunotherapy in this age group. Encouraged by strong outcomes in younger cohorts and early successes in older populations, researchers are actively investigating therapeutic strategies tailored to aging individuals.

Observational registries and retrospective analyses often capture a broader, more representative elderly population and generally show similar or slightly reduced efficacy compared with younger counterparts. Real-world data indicate that elderly patients typically achieve comparable objective response rates, although some studies report a trend toward lower rates of durable response. Clinical trials, however, have revealed that older patients are at greater risk of severe adverse events, such as cytokine release syndrome, which frequently results in early treatment discontinuation and diminished overall benefit. To mitigate these risks, integrating anti-inflammatory agents into immunotherapy protocols could help reduce toxicity. Because aging is strongly associated with a chronic, low-grade inflammatory state, it is critical for future research to assess how this persistent inflammation affects both the safety and efficacy of immunotherapy in older adults. The availability of numerous clinically approved anti-inflammatory drugs presents an opportunity to develop combination regimens designed to counteract dysregulated inflammatory responses. Early findings from both experimental models and clinical studies are encouraging and pave the way for more effective and safer immunotherapy approaches for the elderly.

As novel therapeutic agents and combination strategies continue to emerge, the influence of age as a critical biological variable will become increasingly evident. Future clinical trials should incorporate detailed analyses of age-related factors. Although several aging-associated genes have been proposed as potential therapeutic targets, it is important to recognize that not all are suitable for clinically applicable interventions. Achieving meaningful clinical efficacy will likely require integrating these genetic targets with flexible therapeutic approaches and efficient delivery systems. Some aging-related genes may ultimately function better as prognostic markers or as tools to guide the selection of specific therapeutic agents rather than as direct targets. Caution is necessary, however, because these agents could interact synergistically with other genes and signaling pathways, potentially leading to excessive downstream activation with harmful consequences.

Research on senescence and aging has accelerated significantly, reflecting its broad implications for both gerontology and oncology. While cellular senescence contributes to immunosuppression, tumor immune evasion, and various degenerative disorders, it also plays a central role in tumor progression. Therefore, beyond the current range of age-related biomarkers and diagnostic methods, there is an urgent need to deepen our understanding of senescence. Significant advances are expected through the integration of cutting-edge multi-omics technologies and computational modeling, which can precisely quantify cellular senescence and delineate the complex molecular phenotypes associated with aging. These multidimensional approaches offer a powerful platform for decoding the intricate molecular alterations that occur with age. Ultimately, the convergence of multi-omics data, advanced computational tools, and conventional biomarkers holds great promise for enhancing our understanding of the mechanisms underlying senescence and aging. In addition, clinical trials should prioritize the systematic collection of detailed data on adverse events and treatment responses across different age groups, as such insights remain limited for older patients. This information is essential for determining optimal dosages and therapeutic ranges in the elderly, as well as for developing personalized treatment strategies that account for the unique immune landscape of aging individuals. Recent studies highlight emerging strategies for personalizing ICI therapy in older adults, including geriatric assessment-guided dosing, incorporation of prospective comprehensive geriatric evaluations, pragmatic eligibility models, and protocols driven by biomarkers and frailty assessments[90,93-95]. Ongoing and future research will help refine how best to optimize the safety, tolerability, and efficacy of immunotherapy in this underrepresented population. Furthermore, continued investigation is critical to elucidate the fundamental mechanisms underlying age-related shifts in immune checkpoint gene expression, which may ultimately lead to more precise and effective therapeutic interventions.

Declarations

Authors contribution

Baxevanis CN, Tsitsilonis OE: Article conception and design, writing-original draft preparation, writing-review and editing.

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The authors declare no conflicts of interest.

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