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Review

Immunotherapy in Elderly Patients: A Review

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Abstract

Immunotherapy is a recently developed treatment against most forms of cancer. Although since the early 1990s, many advances have been made with the finding of new drugs as chemotherapy and molecular targeted therapies, the latest drugs approved for cancer treatment are mostly immunotherapy.

These immunotherapies, including drugs directed against immune checkpoint Programmed cell death protein 1 (PD-1), Programmed cell death protein 1 ligand (PD-L) 1, and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), have become a consolidated treatment strategy regarding various kinds of tumors, with an effective response, and good tolerability towards patients. Patients over 65 years old constitute a large portion of the neoplastic population, and are increasingly represented in medical oncology clinics. Unfortunately, however, these patients are underrepresented in randomized clinical trials. We also know that with aging, the microenvironment and immune cells undergo marked changes that are defined by the term immunosenescence. In this review, we will consider the various studies on immunotherapy in elderly patients, while evaluating the subgroup analyses to better clarify the efficacy and safety that immunotherapy shows in this frail population in which the treatment strategy must be carefully selected.

Keywords: Aging, anti PD-L1, cancers, immunotherapy, safety

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Age is a major cancer risk factor, and it is associated with poor prognosis.[1-2] The exciting revolution of development of Immune Checkpoint Inhibitors (ICIs) in Oncology raises high expectations for our elder patients. Indeed, ICIs have been approved for melanoma, non-small cell lung cancer, renal cell cancer and others type of malignancy.[3-8]

Immunotherapy has encountered great results in the treatment of cancer, as in lung cancer where an overall response rate (ORR) of 15% was obtained [9], in urothelial tumors (ORR 25%) [10], in HNCs (ORR 20%) [11,12], gastric cancer (ORR 20%) [13], hepatocellular carcinoma (ORR 20%) [14], ovarian cancer (15%) [15,16], triple negative breast cancer (ORR 20%) [17], mismatch deficient repair colon cancer (ORR 60%) [18], and Hodgkin lymphoma (ORR 65-80%) [19,20], with new indications in progress in different districts. Moreover, ICIs monotherapy obtained an excellent toxicity profile. Half of the patients diagnosed with neoplasia have an average age above 65 years and thanks to the good toxicity profile of immunotherapy, this becomes a good option in curing elderly patients.[21] But the full efficacy and toxicity of these drugs are still widely unknown and unfortunately, in randomized clinical trials, the percentage of elderly patients included is very low. Furthermore, comorbidity and the aging of the immune system can affect the efficacy and tolerability of these drugs. In this review, we will consider the efficacy of ICIs in the elderly population and evaluate toxicities and its management.

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Methods

We have carried out a careful search of the full papers on PubMed (www.ncbi.nlm.nih.gov/pubmed/, accessed on 30 June 2022) starting from 2017, inserting as keywords "immunotherapy, aging, and anti-PD-L1." The full articles found have been reviewed in detail. In addition, all abstracts from international congresses from 2020 to June 2022 were reviewed.

How Targeting Immune Checkpoints Works

Immune checkpoints are a class of receptor-ligand that modulates the immune response. In fact, after the recognition of the antigen by the T cell receptor (TCR), the T-cell response is regulated by suppressor or stimulatory mechanisms influenced by immune checkpoint inhibitors (ICIs). Their function is to maintain self-tolerance, limiting the immune response over time.[22] Unfortunately, cancer cells do acquire the ability to divert the immune system by blocking it with the insertion on the cell surface of immune checkpoints capable of inhibiting the cells of the immune system from recognizing and destroying neoplastic cells. Immune checkpoint inhibitors can restore the immune system, activating, and prolonging the immune system's response against neoplastic cells.[23] To date, many immune check points have been identified, but only a few have found therapeutic use in clinical practice, such as anti-CTLA-4, anti-PD-1, and PD-L1.

Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4)

CTLA-4 is one of the best-known immune check points (ICs). It interacts with TCR, a cluster of differentiation 28 (CD 28). CD 28 and CTLA-4 also share the same ligand: CD 80 (also known B7.1) and CD 86 (also known B7.2). CTLA-4 has a high affinity with ligands. It is expressed on the surface of CD 4 +, CD 8+ T cell and regulatory T cells (Tregs). The hyperactivity of CTLA-4 increases the suppressor function of Tregs, while reducing the production of Interleukin-2 (IL-2) with less expression of the IL-2 receptor. By blocking this immune checkpoint, the T cell cytotoxicity is amplified with simultaneous inhibition of Regulatory T cells (Tregs), stimulating and reactivating the anti-neoplastic function of the immune system.

PD1/ PDl-1 Pathway

PD 1 is another immune check point that is expressed by T lymphocyte cells in peripheral tissues. It recognizes two ligands: PDL-1 and PDL-2, both expressed on antigen presenting and tumor cells. [22-25] This is an immune evasion mechanism, which puts the cancer cell in place to slow down the immune system. This process can be intrinsic through constitutive oncogenic signalling, or secondary to a hyper-production of Interferon gamma (IFN gamma). [26,27] Thus, by inhibiting these immune checkpoints with ICIs, a prolonged response from the immune system can be achieved with a long control of tumor growth.

Immunosenescence and Tumorigenesis

As we age, all organs undergo a slow and gradual process of deterioration. In non-malignant cells, there is a reduction in duplication velocity after a reduced number of passages. [28] Cellular aging is associated with changes in chromatin structure, with excessive accumulation of DNA damage, mitochondrial dysfunction, and reactivation of oncogenes. [29] Unlike dormancy cells, senescent cells still maintain the ability to secrete soluble factors in the surrounding environment, controlling processes that affect inflammation and tumorigenesis.[30] Furthermore, the cellular aging process induces a state of chronic inflammation caused by the secretion of pro-inflammatory cytokines such as interleukin 1β (IL-1β), interleukin 18 (IL-18) and tumor necrosis factor–α (TNF-α).[31] Inflammation also causes some age-related diseases such as cardiovascular disease, degenerative brain disease, and cancer. This process is called inflammaging Figure 1.[32]

The mechanism that causes inflammation is not well known. Immunosenescence determines a continuous remodelling of the immune system with its reduced functioning, even if there are no objective parameters to evaluate this process, and even if the low levels of chronic antigenic stimulation, together with Cytomegalovirus (CMV) infections suggest this.[33] The aging of the immune system determines a reduced immunosurveillance and therefore an increase in the onset of infections and cancer.

Haematopoietic Stem Cell (HSC) Aging

Changes occurring in the HSC are due to impaired immunosurveillance and tumorigenesis. Furthermore, there

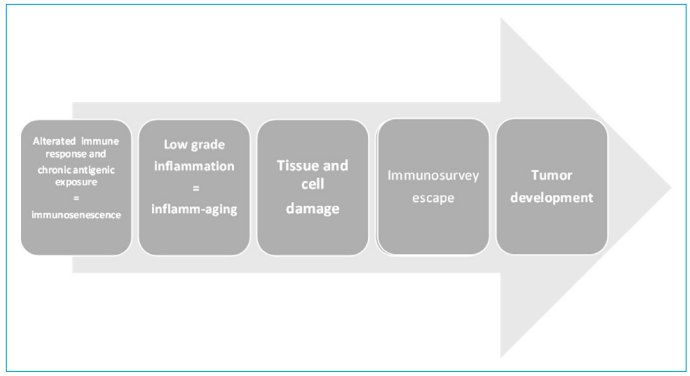

Figure 1. Relationship between immunosenescence and anti tumor immunoresponse.

is also an imbalance in the production of blood elements with a reduction in the lymphocyte share at the expense of the myeloid series.[34-38] This imbalance is caused by the reduction in production of IL 7, produced by stromal cells, an important cytokine that intervenes in the maturation of lymphoid cells.[39] This shift towards the myeloid series, associated with the accumulation of reactive oxygen species (ROS), could also explain the increased occurrence of myeloid leukaemia in the elderly population.[40] The aging of the bone marrow, with an increase in the adipose component, also intervenes in the process of reduced production of the cellular component.[41]

Immunosenescence and Tumor Antigen Release

Cancer cells, over time, accumulate genetic and epigenetic alterations with an increase in the expression of neo–antigens.[42] With the aging process, a reduced capacity for expression of neoantigens has been seen with consequent declined immune response, explained by the impaired response of immune cells to cytokines (IL-2 and IL-12).[43] The changes observed also in the ratios between cells of the myeloid compartment may favour the activation of cells with an inflammatory phenotype instead of a cytotoxic phenotype.[44] Natural Killer cells (NK cells) are another group of immune cells that malfunction during aging. Specifically, a variable NK activity was observed in elderly subjects.[45,46] Furthermore, reduced cytotoxicity of CD 56/CD 16 cells was noted in elderly patients, because of a lower expression of activating receptors such as Natural Killer Cell Receptor 2A (NKG2A).[47] We observed furthermore monocytes/macrophages malfunction with aging with reduced superoxide production [40-50] and decreased antibody-dependent cell mediated cytotoxicity activity.[51] In addition, an increase in danger associated molecular patterns (DAMPs) [52] and a reduction in lymphocytes γδ were observed.[53]

Tumor antigens are processed by cells presented antigens (APCs) with Major Histocompatibility Complex class I (MHC class I) present it to T lymphocytes. Ageing is characterized by a reduction in the number of APCs and a consequent reduction in the adaptive immune response.[54-56] A reduced production of T cells has been demonstrated in the thymus in the elderly.[57] This occurs because the normal stroma of the thymus is replaced by adipose tissue [58,59] with consequent production of pro-inflammatory cytokines.[60] Furthermore, the CD4 / CD8 ratio is altered due to an increase in CD8.[61] After being produced in the thymus, the T cells migrate to the lymph nodes, where they mature. This trafficking has been found to be reduced in older mice.[62] T cells are the main effectors of antitumour immune response. The immunosenescence of these cells has been associated with a poor outcome.[62,63] An increased generation of terminally differentiated or memory T cells and a reduction in effector tumoricidal T cells has been observed with age. This is an important hallmark of ageing. In fact, T cells exhibit senescent changes after 65 years of age [64], leading to reduced T-cell proliferation and cytotoxic activity. Indeed, defective effector cytolytic CD8 + and Th1 CD4 + T-cell differentiation in response to infection in older patients has been reported [65], with decreased expression of perforin and granzyme in senescent T cells.[66]

Furthermore, with aging, an increase in the number of memory cells has been observed, with loss of CD 28 expression and consequent loss of proliferation arrest with increased apoptosis.[67] In addition, the reduction of naïve T-cells is associated with a decrease in the repertoire of the T cell receptor (TCR).[68] On the other hand, no structural changes were observed in the TCR, but downstream signalling events were described.[69] T cells, with ageing, are characterised by a decline in control to kill tumor cells because they are the principal effector of antitumor response. The immunosenescence of these cells is being associated with a poor outcome.[70-71] T cells undergo notable changes during aging even after 65 years [72]; a reduction in activity of CD 8+ and CD 4+ has been shown after an infectious stimulus in elderly patients [73], with reduced production of perforins and granzyme.[74] Furthermore, myeloid-derived suppressor cells (MDSCs) also undergo changes with the process of aging [75], secondary to the increase in pro-inflammatory cytokines [76], with an immunosuppressive activity [77-79], consequent to the increase in Treg.[80] Furthermore, during aging, CD 4+ cells differentiate towards a regulatory phenotype.[81]

Efficacy Data of ICIs in Elderly Patients

In clinical practice, some molecules have been approved by EMA/FDA, such as anti-CTLA-4 (Ipilimumab) and anti-PD-1/ PDL-1 (Nivolumab/ Pembrolizumab). We have a meta-analysis published in 2015 where has been studied ICIs efficacy in older patients compared with younger.[82] This analysis included 5265 patients treated in nine clinical trials, phase III and II, with 5 trials in patients with melanoma, 1 with prostate cancer, 2 with lung cancer and 1 with renal cell carcinoma. Five trials had as cut- off age 65 years, and one had 70 years as a limit between old and young patients (Table 1). In 2078 young patients, the pooled HR for overall survival had a significance difference respect to control (HR, 0.73; 95% CI, 0.66–0.81; p<0.001). In older patients, 1244, in the same way, the pooled Hazard ratio for overall survival of ICIs treatment reached a significance difference regarding the control (HR, 0.72; 95% CI, 0.58–0.90; p=0.004). Moreover, in this meta-analysis, we didn't have differences statistically significant for HR overall survival

Table 1. Outcomes in cancer patients treated by immunotherapy: studies with age group comparisons.

Publication (author, journal, year and study type)	Reference number	Immunotherapy (ies) used	Tumor localisation(s)	Immunotherapy arm n¼	Elderly population		ORRR
					Age groups	n¼	
Elkrief A, J Geriatr Oncol, 2020, retrospective, real life and multicentric cohort	70	Anti-PD-1 and anti-PD-L1 nivolumab, pembrolizum and others	NSCLC	381	<70 ≥70 <65	257 124 339	
Borghaei H, NEJM, 2015, clical trial versus docetaxel, subgroup analysis	72	Nivolumab	NSCLC	582	65e75 ≥75 <65	200 43 79	
Brahmer J, NEJM, 2015, clical trial versus docetaxel, subgroup analysis	73	Nivolumab	NSCLC	135	65e75 >75 <70	45 11 90	16.7%
Gettinger SN, JCO, 2015, phase 1	76	Nivolumab	NSCLC	129	≥70	39	17.9%
Spigel D, J Thor oncol, 2019, phase 3 e4b	77	Nivolumab	NSCLC	1426	<70	870	
Grossi F, Eur J Cancer 2018, multicentric real-world study	78	Nivolumab	NSCLC	371	≥70 whole	556 1426	
Landre T, JCO, 2016, sub-group analysis of pooled published randomized control trials versus standard therapy	71	Nivolumab	NSCLC & RCC	687	<65 65e75 ≥75 whole	126 175 70 371	18% 18% 19% 18%
Motzer RJ, NEJM, 2015, phase 3 versus everolimus	74	Nivolumab	RCC	410	65e75 ≥75	541 146	
Motzer RJ, NEJM, 2018, phase 3 versus sunitinib	74	Nivolumab þ ipilimumab	RCC	425	<65	257	
Ferris RL, NEJM, 2007, phase 3 versus standard chemotherapy	75	Nivolumab	Head and neck	228	65e75 ≥75	119 34	
Balar AV, lancet oncol, 2017, multicentre phase 2, subgroup analysis	83	Pembrolizumab	Bladder	370	<65 65e75	265 125	
Bellmunt J, NEJM, 2017, phase 3 versus chemotherapy, subgroup analysis	84	Pembrolizumab	Bladder	270	≥75 <65	35 172	
Betof AS, the oncologist, 2017, retrospective, 2 centers	79	Anti-PD-1 and anti-PD-L1	Melanoma	254	65e75 <65	56 57	30%
Rai R, annal oncol, 2016, retrospective and multicentric analysis	80	Pembrolizumab and nivolumab	Melanoma	283	≥65 <65	25 105	26%
Robert C, NEJM, 2015, phase 3 versus dacarbazine, subgroup analysis	81	Nivolumab	Melanoma	210	≥65 <50 50e64	165 57 85	
Chiarion Sileni V, J Exp Clin Cancer Res, 2014, multicentric pooled analysis	82	Ipilimumab	Melanoma	833	65e74 >75 ≤75	65 47 256	 1 34%
Kugel CH, clin cancer research, 2018, restrospective multicentric þ preclinical model	88	Pembrolizumab	Melanoma	538	>75 <65 65e75 >75 ≤70 >70 <62 ≥62	35 106 77 27 645 188 238 300	48%

HR: hazard ratio; ns: non significant; NSCLC: non small cell lung cancer; OS: overall survival; ORR: overall response rate; RCC: renal cell carcinoma.

between old and young patient (p=0.93). Another large meta-analysis of 34 randomized studies including a total of 20511 patients, Huang et al. reported that patients aged >65 years derived similar overall survival (OS) (HR 0.79 vs. 0.76) and progression-free survival (PFS) (HR 0.77 vs. 0.69) benefits compared to those of their younger counterparts from immunotherapeutic agents.[83] Patients aged 75 years or more did not derive a definite PFS or OS benefit with ICIs; however, these results may have been confounded by the small number of patients in this age group. Finally, Galli et al. reviewed 290 cases, with a median age of 67 (range: 29–89). Patients aged <70, 70–79 and≥80-year-old were 180, 94 and 16, respectively. Clinical/pathological variables were uniformly distributed across age classes, except for a higher rate of males (p 0.0228) and squamous histology (p 0.0071) in the intermediate class.[84] Response Rate (RR) was similar across age groups (p 0.9470). Median Progression Free Survival (PFS) and Overall Survival (OS) did not differ according to age (p: 0.2020 and 0.9144, respectively). Toxicity was comparable across subgroups (p: 0.6493). The only variables influencing outcome were performance status (PS) (p<0.0001 for PFS, p 0.0192 for OS), number of metastatic sites (p 0.0842 for PFS, P: 0.0235 for OS) and ICIs line (p<0.0001 for both PFS and OS).

Cancer Immunotherapy and Cancer Management in the Elderly

Since the first results of preclinical studies of drugs blocking the PD-1/ PDL-1 and CTLA- 4/CD80 axis have been obtained, there has been a rapid and ever-increasing application in clinical practice such that today the FDA-approved indications are in nearly over 20 different types of cancers. Anti-PD-1 and anti- PDL-1 represent the class of drugs with the greatest use in clinical practice, with nearly 3000 clinical trials both in single agent and in combination with other treatments. Today we have seven anti-PD-1 drugs (Pembrolizumab, Nivolumab, Cemiplimab, Sintilimab, Carmelizumab, Toripalimab, Tislelizumab) and three anti-PDL-1 antibodies (Atezolizumab, Durvalumab, and Avelumab).

Furthermore, combinations of two immunotherapeutic agents or the association of an immunotherapy with chemotherapy, radiotherapy or anti-angiogenic drugs were studied. Studies have tested them in the second or later lines, but now we also have encouraging results in the first line or in the neo adjuvant setting.[83-86]

Having the follow-up data at more than 5 years, we have seen that treatment with immunotherapy prolongs life and, in some cases, we can consider them to be long-survival.[87] The research of PDL-1 levels and microsatellite instability (MSI), allows to better select the patients who respond to immunotherapy, but given the recent results, new response drivers are always sought to better select the patient responders. For this reason, new biomarkers are being evaluated (tumor mutational burden, interferon signature, lymphocyte infiltrate, microbiome).[88-90] Regarding toxicity, anti-PD-1 and anti-PDL-1 are more tolerated than chemotherapy, with a few G3-G4 toxicities. Instead, drugs that act on the CTLA-4/CD 80 axis are more toxic.[91,92]

Elderly and Treatment

From the data of the national cancer statistic institute, the average age of onset of tumors is 65 years: 70 years for lung cancer, 63 years for melanoma, 64 years for kidney cancer, and 71 for colon cancer.[93] Despite the lengthening of the average life span of the population, the elderly are still underrepresented in randomized clinical trials.[94,95] So, we do not have the risk versus benefit results in this population. In geriatric patients, comorbidities, organ dysfunction and geriatric syndrome heavily influence treatment outcomes and toxicity. Therefore, there is less scientific evidence in this patient setting, leaving open issues for oncologists who must deal with oncological disease in patients where chronological age often does not coincide with clinical conditions.

It is very important to use tools that can give us clear information on the real clinical conditions of the elderly in order to intensify or reduce the oncological treatment.[96] For this reason, scientific societies recommend the comprehensive geriatric assessment (CGA) to evaluate multi domain health problems capable of influencing treatment outcomes.[97] These tools evaluate together the social, nutritional, cognitive, and behavioural status, together with comorbidities. Using the collected data, the oncologist can treat the elderly patients with standard treatment or with a dose reduction, adapting therapy to the clinical condition, or referring them only to best supportive care (BSC).[98]

Elderly and Response to Immunotherapy

In the elderly, where the immune system has lost its function, with a response in which type B cells, Natural killer (NK), and dendritic cells (DC) are involved, considering that they respond less to vaccination, it could be that they respond consequently less to drugs that block the PD-1/PDL-1 or CTLA-4/CD80 axis.[99] However, there are still doubts about the efficacy of immunotherapy in patients over 75 years of age, especially regarding the response compared to the organ under consideration. In pivotal phase III trials, we have immunotherapy patients not responders over 75 years old, in non-small cell lung cancer, metastatic renal cancers, and in tumors of the upper GI.[98-109] However, other studies carried out in non-small cell lung cancers have

shown an advantage in immunotherapy even in patients over 70-75 years old.[110-112]

In metastatic bladder cancers and metastatic melanomas, no differences were observed between elderly and younger patients.[113-118] Specifically, anecdotal responses have been observed in 90-year-old patients with metastatic melanoma, associating anti-PD-1 with anti-CTLA-4.[119] But in some studies of metastatic melanomas in the elderly aged 60-80 years, a better response to immunotherapy was observed [66,67] with a greater number of CD 8+ cells respect to regulatory T cells (Treg).[120] A possible explanation for this paradoxical result is that elderly patients have a greater burden of antigenic mutations, linked to the long period of exposure to carcinogenic agents.[121]

Immunotherapy and Toxicity in Elderly

Since in animal models, immunotherapy treatment showed a high rate of toxicity in elderly mice, this aspect was carefully controlled in randomized clinical trials, where an equal level of G3 toxicity was observed in elderly and young patients.[122] This was noted both in monotherapy with anti-PD-1, PDL-1, and anti- CTLA-4 and in anti-PD-1 and anti-CTLA-4 combination, even if in various studies considered the threshold age for defining an elderly patient between 70 and 80 years, demonstrating that there is no threshold value. [93,123-126] However, a limited number of trials have shown greater toxicity in patients over 80 years of age treated with anti-PD-1 in combination with anti-CTLA-4. [126,127] Furthermore, in many works, a phenomenon called hyper-progression has been highlighted during treatment with immunotherapy, with variable frequency depending on the authors and the tumor location.[128,129]

Although there are different results, in one of them, older age correlated with a higher frequency of hyper-progression during treatment with immunotherapy [128]. Even if the percentage of side effects in elderly patients has been the same as that of younger, the different impact in the elderly population has to be still considered, given the reduced functional reserve of the various organs of this vulnerable population. However, there is great evidence that immunotherapy is less toxic than chemotherapy in the elderly.[130]

Conclusion

All studies to date, have shown that immunotherapy is safe and effective in patients under 75 years old. On the other hand, contradictory data are present in the elderly population over 75 years old because of a very small number of this population represented in randomized clinical trials. Furthermore, in these patients, the response also depends on the tumor location. Consideration should be given to the high bias caused by the small number of patients and the retrospective nature of many studies. Furthermore, the threshold for defining elderly patients varies from study to study with values ranging between 70 and 75 years, making the meta-analysed data not very homogeneous and difficult to understand. Furthermore, in the clinical trials, the conditions of the patients were only evaluated with the Performance Status (PS), without performing any multidimensional evaluation tests. However, the subgroup data of pooled analysis comfort in the use of immunotherapy in elderly patients, where the efficacy has been found to be comparable in respect to the younger population. The toxicities also seem to be the same between the elderly and the young population, although in subjects over 80, the combination of anti-PD-1 / PDL-1 with anti-CTLA-4 showed greater toxicity. Over the years we have learned to manage these toxicities other than those induced by chemotherapy, also drawing up guidelines.

It is desirable, in the future, to be able to perform randomized clinical trials with ICB in the elderly population over 75 years old.

Disclosures

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