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REVIEW

Does patient age influence anti-cancer immunity?

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Abstract

Geriatric oncology, important for the ever-increasing numbers of elderly cancer patients, has thus far focused primarily on tolerance to chemotherapy. With the advent of breakthrough immunomodulatory antibody treatments relying on the patient's own immune system to control the tumor, the issue of immunosenescence becomes extremely important. There is increasingly a valid concern that anti-cancer immunity may be compromised in the elderly due to (i) their low amounts of naïve T cells (potentially leading to holes in the repertoire for neoantigens), (ii) "exhaustion" of potentially tumor-specific memory T cells, and (iii) higher amounts of suppressive cells. Encouragingly, but only anecdotally, accumulated clinical experience suggests that advanced age does not result in poorer responses or greater toxicity in elderly patients treated with anti-CTLA-4 or anti-PD-1/PD-L1 antibodies. Here, I briefly contrast immune features of the elderly with the young, commonly referred to as "immunosenescence," and the influence of patient age on the outcome of checkpoint blockade. As newer agents are licensed, and new combinations tested, broader and more detailed studies focusing on the age question will be crucial and should be taken into consideration when designing clinical trials.

Keywords Checkpoint blockade · Immunosenescence · Melanoma · Anti-CTLA-4 · Anti-PD-1/PD-L1 · Geriatric oncology

Introduction

What is human "immunosenescence"?

This review begins with a brief overview of the impact of age on the human immune system. It will not refer extensively to the many studies in animals, especially mouse models, because of their mostly limited applicability to clinical cancer treatments. The process by which the immune system is believed to become less able to function optimally is commonly termed "immunosenescence." However, this is an imprecise term which should be reserved for describing age-associated changes to immunity that are proven to be associated with negative clinical outcomes, and which do not simply reflect differences between young and old people. Many of these are the result of adaptive responses to earlier challenge throughout life, rather than being degenerative [1]. Thus, although it is clear from a multitude of studies that essentially all measures of innate and adaptive immunity are different in younger and older people, their actual clinical impact is mostly obscure, and markers for assessing the immunosenescent state are problematic. Most published studies, the majority of which are cross-sectional (and therefore can only determine differences and not changes), do not provide evidence that observed age-associated differences in immune parameters measured are indeed detrimental. In fact, one often reads in the literature that, e.g., "T cells are the main effectors of antitumour immune response. The immunosenescence of these cells has been associated with a poor outcome" [2] in this instance citing papers by Wikby et al. [3, 4]. In fact, these two papers do not refer in any way to anti-tumor immunity and scouring the literature reveals little to support this statement—in humans; in mice, the situation is different, as reported by many investigators (for a recent review, see [5]).

With this in mind, there follows a précis discussing age-associated differences in peripheral immune parameters and their potential clinical impact in humans.

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Hematopoiesis in the elderly

The hematopoietic stem cell (HSC) compartment in the bone marrow (BM) is required to provide all blood cells over the lifespan. Clear differences between young and old people might therefore be traced back in the first instance to alterations in the stem cell niche and/or the HSCs. This has not been robustly demonstrated in humans, although hematopoiesis may be monoclonal in very late life, which might a priori be expected to have some effect on immunity and is certainly known to have negative health implications [6]. Thus far, it is only in mice that definitive evidence for a deleterious effect of intrinsic HSC aging on T and B cell status has been forthcoming. In an elegant recent paper, Leins et al. showed that the negative effects of aging on these cells could be reversed by inhibiting their higher Cdc42 activity and that this restored the animals' capacity to mount as strong an immune response to vaccination as young animals [7]. Whether the same is true in humans remains to be seen at this time, although the potential importance of cdc42 for certain other health outcomes is now emerging [8, 9].

Innate immunity in the elderly

Phagocytic cells

Aging in humans is commonly accompanied by increased infectious and inflammatory disease, associated with a higher basal inflammatory status than in the young, as determined by levels of factors such as IL-6 and TNF in the blood (this has been dubbed "inflamm-aging" [10]). Much of this may be due to differences in myeloid phagocytic cell functions manifesting as higher basal free radical and pro-inflammatory cytokine production but paradoxically lower capacity for defending against pathogen challenge [11]. Under certain as yet still ill-defined circumstances, myeloid cells may become arrested at early maturation stages and exert suppressive effects on immune responses. There is some evidence that the levels of such "myeloid-derived suppressor cells" (MDSC) may also be higher in the elderly than in the young [12].

Natural killer cells

The number of peripheral natural killer cells (NK cells) is generally higher in the elderly, possibly associated with the presence of higher levels of cells with the more cytotoxic CD56dimCD16+ phenotype. There may be a lower expression of the activating receptors NKp30 and NKp46, and the co-stimulatory DNAX (DNAM)-1 molecule, by NK cells from the elderly, resulting in poorer function on a per-cell basis [13].

Dendritic cells (DCs)

There are two major DC lineages, monocytic DCs (mDC) which present antigen to T cells, and plasmocytoid DCs (pDCs) which are crucial for defense against viruses via rapid type I interferon (IFN) production. Any age-related differences in humans are likely to be subtle, but it has been reported that DCs from the elderly have a compromised ability to stimulate naive CD4+ T cells [14].

Adaptive immunity in the elderly

B cells

B cells generated from HSCs in the BM are released to the periphery as mature cells. They undergo two phases of development, first prior to their recognizing antigen, and later after activation. Mature B cell production takes place exclusively in the BM, with immunoglobulin gene rearrangements generating a large repertoire of B cell antigen receptors (BCRs) expressed on the cell surface. Some evidence suggests that this process is less efficient in older animals and potentially also humans [15]. After stimulation by antigen and with help from T cells, B cells undergo clonal expansion, and controlled mutation of the BCR to select those with a higher antigen affinity. As they mature, B cells switch from producing IgM to IgG or other Igs and an increase of memory cells relative to naïve cells. This is the major age-associated change, which is clearly adaptive. Nonetheless, there is some evidence that in addition to this normal function of adaptive immunity, other aspects of B cell immunity may be compromised with age [16].

T cells

Unlike B cells, T cell progenitors are not functionally mature when released from the BM into the periphery, but must be further processed in the thymus, which is very active early in life, but rapidly reduces in size and output after puberty. Adult humans retain only residual thymic function, and this is all but absent in the elderly. The naïve T cells generated by thymic selection and maturation early in life must provide protection against the onslaught of novel pathogens encountered in infancy and childhood. Thereafter, memory cells are required to protect against rechallenge, and the necessity for a broad naïve T cell repertoire decreases. These are physiological phenomena, on which adaptive immunity depends. Due to thymic involution, and lower amounts of T cell progenitors from the BM, very few naïve T cells are produced in later life. Thus, the elderly individual will mostly rely on the adaptive immune cells already formed in early life. The presence of fewer naïve T cells with a restricted TCR repertoire, reciprocated by the larger amount of memory T cells is universally

observed with aging. Moreover, elderly people commonly possess very marked expansions of late-stage differentiated memory cells, especially CD28-negative, CD27-negative CD8+ T cells, which are often referred to in the literature as "senescent," and the accumulation of which has been associated with numerous negative clinical outcomes [17].

Immune responses against primary antigenic challenge not only require the presence of T cells carrying TCR capable of binding peptide/MHC complexes, but also appropriate activation signals for the clonal expansion of naïve T cells to generate effector and memory cells. This is orchestrated by a complex network of strictly regulated signaling molecules which may be differently affected by the aging process. Thus, many downstream events of TCR signaling seem to be impaired in the elderly, including the activity of key components of TCR signaling, such as the balance between Lck and opposing signals mediated by the CD45 protein tyrosine phosphatase (PTPase) and by cytoplasmic Csk [18]. Numerous attempts to modulate T cell responsiveness are aimed at restoring these signaling pathways to restore appropriate immune function [19]. Additionally, several studies suggest that levels of regulatory CD4+ T cells with immune suppressive properties (Tregs) may increase with age and further dampen any immune reactivity [20]. At the same time, the integrity of both naïve cells and memory cells is compromised as a result of their residing in the elderly environment for an extended period of time [21]. The reason for this apparently negative effect of the systemic elderly environment is currently under intense scrutiny [22].

Immune correlates with response to vaccination in the elderly

The features of immunosenescence outlined above merely described some of the differences observed in immune parameters assessed in peripheral blood. Little is known about the impact of aging on tissue-resident immune cells, although this is slowly beginning to change [23]. Hence, with some exceptions, data in humans assessing immune correlates with any clinical outcome are mostly based on assays of biomarkers in peripheral blood. The most obvious correlates to examine in the non-cancer arena, are susceptibility to infectious disease, and mortality. For example, numbers of IgM memory B cells are lower in the elderly, correlating with lower anti-pneumococcal responses [24]. Many studies implicate T cell dysfunction associated with the perceived poorer responses of the elderly to seasonal influenza vaccination, suggesting malfunction of both T cell help to antibody-producing B cells, as well as cytotoxic T cell deficiencies [25]. Improving immune responses to vaccination would clearly have a large impact on clinical medicine, including cancer vaccine programs. Better understanding of the reasons for poorer responses in the elderly would assist in the development of improved approaches in the elderly. Obviously, vaccination can only be effective when DC antigen presentation is intact, and functional T and B cells with appropriate antigen receptors are present, in the absence of excessive Tregs and MDSCs. All of these parameters are different in the elderly, as outlined above. Surveying the data emerging from clinical trials with the major licensed immunotherapeutics anti-CTLA-4, anti-PD-1, and anti-PD-L1 antibodies, enables us to ask whether any of the parameters different in the elderly correlate negatively with clinical outcome of these treatments.

Survey of cancer immunotherapy outcomes in older patients

Although there seem as yet to be no reported clinical trials specifically targeting elderly cancer patients for checkpoint blockade treatment, many older patients have been included in such trials, and in some cases also in reports of treatments outside of the controlled clinical trial context (i.e., in the "real world" setting). For historical reasons, the majority of available data stems from late-stage melanoma patients treated with anti-CTLA-4 antibodies, and more recently anti-PD-1 antibodies. Data on other cancers and treatments are rare, but in the meantime there are now reported results especially for non-small cell lung cancer (NSCLC), but also for bladder, renal, head and neck, gastrointestinal and gynecological cancers.

Impact of patient age on outcome of treatment of melanoma with checkpoint blockade

Clinical responses

One of the first reports on survival of a large cohort of stage III or IV melanoma patients treated with the anti-CTLA-4 antibody ipilimumab (ipi) already documented that overall survival (OS) was identical after stratification at age 65 years [26]. In this phase III trial, leading to FDA approval the following year, treatment with single-agent ipi resulted in a 12 month survival of 45.6%, decreasing to 33% at 18 months and 23.5% at 24 months ($n = 137$). OS was reported to be independent of age, sex, or baseline serum lactate dehydrogenase (LDH) levels (although fewer patients with elevated LDH levels survived, this was not significant). Interestingly, survival was only slightly better in this report than in subsequent "real world" situations with potentially less highly-selected patients. Thus, a study seeking predictive biomarkers in a discovery cohort of Dutch patients and a validation cohort of British patients yielded an OS of 37.8% at 12 months and 22.9% at 24 months, again with no impact of age over the range 18–88 years but this time with baseline LDH levels predictive of survival [27]. Other trials report similar results

with ipi for melanoma in patients over 70 or even over 80, with a median OS of 8.9 compared with 7.0 months in those under 70 years of age [28].

Fewer results using anti-PD1 or anti-PDL-1 antibodies have been reported in the aging context, but where older patients have been included it seems that as with anti-CTLA-4, age has little effect on efficacy [29, 30]. Intriguingly, a very recently published single center study of 99 patients with a mean age of 80 prior to any immunotherapy (range 75–92), suggested that clinical benefit in these elderly might even be better than expected from the experience of the center in younger patients [31]. In our own studies (3 centers, 128 patients), we have noted that chronological age itself did not affect OS (taking 70 years of age as the cutoff). However, generally, the proportion of people infected with cytomegalovirus (CMV) increases with age, such that any effects of CMV can be confounded with the effects of age itself, unless adjusted for CMV infection rate. Thus, we have recently found that CMV-seropositive patients tended to have better OS than uninfected patients. Although this survival difference was not statistically significant it became so if patients were stratified according to certain peripheral blood immune cell phenotypic markers known to be sensitive to age and CMV. Thus, relative proportions of NK cells and CD8+ effector memory cells, when and only when taken together with CMV serostatus, were informative as predictive biomarkers of OS on anti-PD-1 treatment of advanced melanoma (J. Bochem et al., manuscript in preparation). These and other data are consistent with a published study in an animal model investigating potential reasons for superior results in the elderly, as determined for anti-PD-1 treatment in several centers [32]. Thus, a survey of a large number of melanoma patients (> 500 from 8 centers) revealed that the rate of progressive disease (PD) was 48% in younger patients but 37% in patients older than 62 years of age, and that the rate of complete response (CR) was independent of age (13 and 15%, respectively). The mouse model employed by these authors indicated that anti-PD-1 treatment significantly improved the control of tumor growth in old animals but not in young ones. This was due to more regulatory T cell (Treg) infiltration but less CD8+ T cell infiltration into tumor lesions in the young animals; treating them with Treg-depleting anti-CD25 antibodies converted the response of the young mice to that of the older mice not treated to deplete Tregs. The authors then went back to the clinic to document fewer Tregs and more CD8+ T cells in elderly patients´ tumors, which may have been responsible for the better response to anti-PD-1 treatment [32].

Toxicity

Although concerns have been raised that toxicity may be more serious in elderly people treated with ipi [33], systematic analyses suggest that based on a survey of 858 melanoma patients over 65 years of age (mean 75 at treatment initiation) 178 pts. (20.7%) suffered severe immune-related adverse events (AE). These were colitis (17.5%), hypothyroidism (10.5%), dermatitis (5.4%), and hypophysitis (3.7%). These data are very similar to those reported for all patients treated with ipi, suggesting that toxicity is not worse (but also not better) than in younger patients [34]. Moreover, in centers treating older patients, data suggest that even in people over 80 years of age, serious AE occur at the same rate as previously reported in younger patients [35]. This has been noted in several studies [28], although some have noted more toxicity in very old patients (over 80) [36].

Data on cancers other than melanoma

A meta-analysis of 5265 patients from 9 trials (up to September 2015) had already indicated that stratifying patients for age > or < 65–70 years, OS rates were essentially identical (despite PFS rates being somewhat better in younger patients) [37]. These results were updated and confirmed in a recent meta-analysis, indicating the robustness of these findings [38]. A recent broad survey of a single-center experience between 2012 and 2016 analyzed the results of 14 phase I/II trials in NSCLC, bladder, renal, head and neck, gastrointestinal and gynecological cancers which included 46 patients over 70 years of age and 174 younger patients. Median OS was 7.1 months in the older group-vs-9.8 in the younger patients, with more toxicity in the former but no difference in severe AEs. Hence, in this very heterogeneous cohort, elderly patients did not differ significantly from younger patients [39]. There are probably most data on NSCLC and RCC in phase III, which are consistent with there being little or no effect of patient age either on toxicity or efficacy [40, 41]. However, in accord with the data on melanoma, there is some evidence that older NSCLC patients not only do at least as well as younger patients, but may do better. Thus, in a study of 117 patients with squamous NSCLC treated with nivolumab of which 59 were over 65 years, the overall response rate was 17% in the latter and 12% in younger patients [42]. In fact, in 4 of 5 trials examined in a recent review, older NSCLC patients did better on anti-PD-1/PD-L1 therapy than younger patients [43]. These and other data are clearly anecdotal, but accumulating experience is pointing in the direction that the (albeit low frequency of) clinical benefit may actually be somewhat higher in the elderly.

What correlates with beneficial therapy outcomes in the elderly?

In our attempts to identify biomarkers predicting responsiveness to ipi treatment in late-stage melanoma, we found that not only did age little influence clinical outcome, but the baseline

parameters informative for predicting responses, as well as their changes during treatment correlating with clinical benefit were also not affected by age [44, 45]. If it is true that clinical benefit of checkpoint blockade is at least as good (or poor) or in the elderly as in younger patients, this implies that aging of the immune system is irrelevant for this type of therapy. If in some cases, outcome is actually better in the elderly, it is clearly of great interest to determine the mechanisms to guide interventions to improve the results, as alluded to in the studies mentioned in "Clinical responses." One other suggestion that can be made to explain the difference between young and old is that the tumors themselves are different in the elderly in that they may have more mutations, due to a longer period of exposure to environmental and/or intrinsic mutagens. If so, they might have more neoantigens which can be targeted by naïve T cells of the host immune system, as elegantly demonstrated in a small number of patients very recently [46, 47]. However, because a major hallmark of immunity in the elderly is that they possess few CD8+ naïve T cells with a shrunken antigen receptor repertoire for neoantigens (see "T cells"), this may present a challenge for developing such approaches in older patients. However, thus far, this concern remains entirely speculative as there are no data on whether the ability to recognize tumor neoantigens is indeed compromised in the elderly. In humans, surprisingly, there are rather few reports formally documenting that responsiveness to any neoantigens is compromised by paucity of naïve T cells. Mostly, this remains an assumption, due to shrunken TCR repertoires. However, where studied specifically, data are available confirming that this is the case, for example, in responses of the elderly to yellow fever vaccination [48]. However, should the lack of neoantigen-responsive naïve T cells indeed prove problematic for immunotherapy of elderly patients, several approaches could be envisaged theoretically to overcome these difficulties, such as adoptive immunotherapy with T cells carrying transfected TCR specific for the respective neoantigen.

Nonetheless, because responses to other tumor antigens such as lineage antigens, cancer testis antigens (the so-called "shared tumor-associated antigens" (TAAs)) are more likely to be memory responses, the immune system of the elderly is more likely to have retained the ability to respond to these. Indeed, we have noted that old breast cancer patients who have retained the ability to mount in vitro T cell responses to her2 peptides experience a survival advantage over those who fail to do so [49]. This was associated with their possession of relatively fewer MDSCs [49] and relatively more pDCs [50] than in patients surviving for a shorter period of time. Because the relative importance of effector T cell targeting of neoantigens-vs-shared TAAs-vs other potential antigens is not clear, and is quite likely to differ from patient-to-patient, for optimal results, individualized approaches are going to be necessary to tailor the particular immunotherapeutic approach to each patient. If this is feasible, the chronological age of the patient will become less important than the level of that individual's immune competence, which will be affected by age in a manner automatically taken into account when determining the best treatment strategy. The technology to accomplish this is in reach or can feasibly be expected to become within reach soon; but it may take longer to ensure that the resources available to health care systems enable each patient to receive such optimal therapies. Thus, the necessary TCR "missing" from the repertoire could be identified and genetically engineered specific T cells could be generated for adoptive therapy which would be able to reconstitute the lacking specific CD8+ cytotoxic T cells in the patient [51, 52]. Despite the major technical but also non-technical hurdles constraining such an approach, there may nonetheless be economic as well as medical arguments for developing such therapies, as even very expensive immunotherapies may still offer a cost-benefit [53].

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