Pharmacologic Modulation of the Immune Response Against Tumours in the Elderly

Juan Bautista De Sanctis

Abstract

Despite the high incidence of cancer in the elderly, little is known about the protective immune response against cancer and the treatment of other comorbidities. Inflamming has been defined to explain a protective inflammatory response in the elderly. New subpopulations of stem cell memory T cells seem to be responsible for a quick memory response to antigens and probably against tumours. Biological immune therapy with anti-checkpoint inhibitors could be an essential tool to treat patients; however, adverse or toxic events are often observed in elderly patients. Several medications used in the elderly, metformin and valproic acid, have been shown to have anti-neoplastic effects. These effects suggest that therapeutic approaches in the elderly should be carefully analysed. Clinical trials are required to assess the exact role of immune response and therapy in tumour incidence and survival in the elderly.

Keywords

Immune response · Elderly · Checkpoint inhibitors · PD-1 · CTLA-4 · Adverse reactions · Metformin · Valproic acid · Comorbidities

J. B. De Sanctis (✉)
Faculty of Medicine and Dentistry, Institute of Molecular and Translational Medicine, Palacky University Olomouc, Olomouc, Czech Republic
Faculty of Medicine, FOCUS Center of Excellence, Institute of Immunology, Universidad Central de Venezuela, Caracas, Venezuela

© The Editor(s) (if applicable) and The Author(s), under exclusive licence to Springer Nature Singapore Pte Ltd. 2020
H. S. Tuli (ed.), Drug Targets in Cellular Processes of Cancer: From Nonclinical to Preclinical Models, https://doi.org/10.1007/978-981-15-7586-0_8
8.1 Introduction

The incidence of cancer in the elderly has always been a matter of discussion [1, 2] (https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence). The documented decrease in immune vigilance, along with the increase of inflammation markers, has generated interest in the field [3–5]. Modulation of immune response by vaccination has been considered appropriate therapy for rescuing memory against infectious diseases [6]; however, in cancer, more sophisticated strategies have to be analysed [7]. The increased susceptibility to infections in the elderly is a clear indication of an impaired innate immunity which, as a consequence, leads to a decreased response of adaptive immunity [3–5]. It is expected that ageing will predispose individuals to a less anabolic and catabolic activity which would limit the response of cells and tissue to injuries. One biological mechanism that partially compensates this phenomenon is inflamaging [3–5]. Inflamaging is defined as a dynamic protective response in which pro-inflammatory mediators and circulating primed cells are increased without generating a clinically perceptible inflammation [3–5, 7, 8]. This pro-inflammatory response is a quick adaptive response observed in healthy elderly individuals. It is often underestimated, it could be modified by therapy, and it partially protects from tumour growth [7, 8]. Thus, the immune response of the elderly should be considered different from healthy adults and infants.

Cancer is frequently diagnosed in the elderly, with approximately 50% of patients being over 70 years of age [1, 2] (https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence). According to the British cancer organisation, female rates of cancer are lower than male after 75 years, and there is a drop in cancer incidence after 85 years (https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence). Tumour screening is either decreased after 85 years or healthy elderly individuals that have an efficient immune response live longer and dye of other natural causes.

In solid tumours, one of the most common cancers in males is prostate cancer and in women breast cancer; however, in both genders, the second most common is lung cancer [1, 2] (https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence). Leukaemias and lymphomas are also prevalent in the elderly population [1, 2] (https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence). One of the hypotheses in geriatric oncology is that continuous replacement of circulating T cells from the bone marrow, impaired genetic control mechanisms, and the absence of thymic selection increases the probability of generating tumour cells (lymphoma). Patients with mild immune deficiencies and some with acquired immunodeficiencies are prone to develop B cell lymphoma. Others in minor extent develop monocytic leukaemia. Nonetheless, patients that had an incipient or surgical removed tumour may present new tumour growth in the same organ or other organs due to the reactivation of dormant metastatic cells which have not been contained by the immune system [9, 10]. This late group is now carefully monitored by the oncologists due to the marked increase in documented cases [1, 2] (https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence).
Usually, studies that involve tumour therapy or immune tumour therapy do not include elderly individuals [11–15]. It is assumed that most of the elderly individuals have comorbidities; however, there is a group of healthy individuals with an adequate response to pathogens and tumours who have been overlooked [7, 8]. This group may provide new pieces of evidence for immune modulation, which can be useful for the treatment of elderly patients with incipient tumours and tumour survivors with a high risk of metastatic tumours. Due to the marked increase in the elderly population, pharmaceutical companies have started programs to monitor different treatment options.

8.2 Protective Immune Cell Populations in Healthy Elderly

Most of the innate immune response in elderly individuals is partially unresponsive to stimuli [3, 4]. The unresponsiveness is generally due to a decrease in signal pathway activation and a reduction in cytokine secretion [3, 4]. The vigilant tissue immune cells in ageing are slow in the generation of resolution mediators which paradoxically provide a mild advantage on alert immune responses [3–5]. Due to the reduced innate response, adaptive responses, based on memory, take charge of the immune response to many known antigens [7, 8]. Nonetheless, the immune challenge with vaccines has proven a useful stimulation of innate immunity providing a more sustained and effective memory response [6, 16].

One of the hallmarks of healthy ageing is the increase in CD4 cells, the decrease in CD8 cells, and an increase in T reg cells with an increase in PD1 [3–5, 7, 8]. The markers of senescence are expressed predominantly in the CD8 population suggesting that crucial antiviral and antitumour response is partially impaired [7, 8]. Several reports in mice and humans have indicated that this decrease in T cell population is assumed by NK cells, NKT cells, or Tγδ cells although this point is still under discussion [3–5, 7, 8, 16].

In healthy elderly individuals, antigen responsive T cells are composed of central memory T (TCM) cells (CD45RO + CCR7+), effector memory T (TEM) cells (CD45RO + CCR7−), and effector T (TEF) cells (CD45RO-CCR7−) [8]. After continuous antigen stimulation with age, a shift in the T cell subset distribution from naïve T cells to TCM, TEM, and TEF. This process is characterised by the loss of expression CD27 and CD28, which may be accompanied to a higher risk of infections, chronic diseases, and cancer [7, 8]. However, a cell population co-expresses CD28, CD95, CD45RO+, and CCR7+ and has been defined as stem cell memory T cells (TSCM) respond quickly to antigen, generating an active immune response [8]. This population seems to originate from the follicular compartment, and they are released to compensate for a decreased number and function of T cells [17]. Thus, effective T cell responses in healthy ageing can be observed and do not represent the majority of the circulating T cells encountered.

Endogenous glucocorticoids produced in stress conditions and ageing induce a decreased immune response in the elderly [18]. Predisposition to chronic diseases or inflammation along with the lack of exercise, non-proper nutrition, and dysbiosis...
may generate this increase [18]. Behavioural changes can affect the production of glucocorticoids. In mice, unaligned chronic circadian rhythm expedites immune senescence suggesting that simple changes in behaviour may alter immune response which increases the susceptibility to lack of immune response which, in turn, would predispose to more probability of tumour growth [19].

One of the most common infections observed in the elderly population is cytomegalovirus infection (CMV). The infection induces a decrease in the expression of CD28 and NK cell activity making the patient more susceptible to other viral infections and the development of tumours [20]. Different T cell responses are also impaired [21, 22]. However, in some elderly individuals, the immune response is restored, which suggests that genetics plays a significant role in the process [23]. Challenging the immune system with vaccination could provide valuable clinical evidence to assess the individual capacity to respond to pathogens and tumours. One could envision that those elderly patients, survivors of cancers that do not respond to vaccines, tumour reappraisal may occur. Vaccines are then an indirect but essential tool for clinicians to assess effective immune responses. Figure 8.1 represents the main differences between the typical healthy adult immune response and inflammaging observed in the elderly population.

8.3 Chemotherapy and Toxicity

Toxicity due to chemotherapy is frequent in elderly patients [14, 15]. Cytokine storm can be generated in these patients due to a marked increase in cell death. This uncontrolled amount of cytokines can be avoided by treating the patients with steroids or additional immunosuppressants to decrease the inflammatory burden. Adding steroids to the treatment jeopardises the protective immune response, moreover, if the patient has comorbidities, it may aggravate them [14, 15].
stress-induced response prolongs hospitalisation, deteriorates the immune response, and the patient is more susceptible to infections. Elderly patients are very labile.

Biological therapy against PD1 and CTLA-4 in elderly patients may not be as effective as in other ages [13, 14]. There are no general guidelines for elderly patients [14, 15]. As aforementioned on T cell populations, the amount of highly active stem T cells in the elderly may be pushed to apoptosis with the anti-checkpoint inhibitors. Thus, checkpoint inhibitors may generate highly toxic side effects in elderly patients by enhancing cytokine storm [13]. These adverse events have been identified as immune-related adverse events (irAEs). The report from the European Society for Medical Oncology (ESMO) differentiates side effect of checkpoint inhibitors, grade 1 and 2 toxicities [24]. The recommendation is to suspend the treatment and monitor the events or start symptomatic or local therapy. The majority of symptoms appear after 4 h. of the initial treatment; however, the manifestations can occur during treatment and be maintained after several months after the treatment has been stopped [13]. Since there may appear skin manifestations, most clinicians would prescribe antihistaminics. In some cases, antihistamines in the elderly give more side effects affecting consciousness and fluid retention deteriorating the patient [25]. If the adverse effects escalate, corticosteroid therapy is recommended (some grade 2 and grade 3 and 4 toxicities). If there is no improvement, more aggressive immunosuppressive therapy is used [24]. In conclusion, biological therapy should be carefully managed in elderly patients.

One of the proposed options in elderly patients is to the use of JAK inhibitors for tumour treatment. However, as suggested after the COVID 19 outbreak, the use of JAK inhibitors could be more detrimental than effective since they would inhibit immune response [26].

8.4 Other Medications that May Affect Tumour Growth and Immune Response

Recently, commonly used drugs in the elderly have been used to treat cancer since some important mechanisms of the compounds have been studied in more detail.

It is well known that hyperglycemic states reduce immune response, and glycemic control restores the effectiveness of the immune system. Metformin is an old drug that has been used in patients with increased insulin resistance and type 2 diabetes for glucose control [27]. The rationale of using metformin in cancer is to decrease the uptake of glucose by the tumour, inhibit rapamycin, enhance mitochondrial control of cell cycle, and eventually induce death by inhibiting autophagy and enhancing apoptosis [28]. Tseng et al. demonstrated that diabetic patients that use metformin had a better survival of lung cancer than their counterparts [29]. On the contrary, diabetic patients without strict glycemic control are prone to have higher tumour growth. Insulin, a known modulator of the immune response, is able to restore immune response at the concentrations normally used to control glycaemia [30, 31]. Hypoglycaemia in the elderly, it is a very dangerous condition, and in patients with cancer with controlled insulin levels is considered a bad prognosis.
Since cholesterol synthesis has been related to tumour growth, treatment with statins was proposed as adjuvant therapy [32]. Perhaps due to the complex metabolism of tumours, no major direct effect has been described. Simvastatin has been studied for breast cancer as an inhibitor of signal pathways related to triple-negative breast tumours [33]. However, the most striking responses on statins and cancer come from trials with diabetic patients in which the use of statins, the best rosuvastatin, seem to enhance a protective immune response increasing patient survival [34]. One may conclude that clinical trials related to the use of statin in elderly patients with cancer should be performed in order to ascertain the effectiveness of these drugs as adjuvant therapy.

Valproic acid (VA), a known anti-epileptic drug also used to treat bipolar disorder, has been shown to a potent demethylating agent useful in cancer therapy [35]. In principle, VA was shown to decrease monocyte to dendritic cell maturation and affect some of the macrophage and NK cytotoxic responses; however, VA increases NK cytotoxic receptors enhancing a specific antitumour response [35]. Most probably these contradictions arise from the in vitro assays as compared to the in vivo assays. The slower clearance of the drug in the elderly [36] suggests that lower doses of the compound would be more therapeutic than higher doses which in fact would decrease immune response efficiency.

There are other medications usually used by elderly patients; however, the lack of relevant data prompted us not to comment on it.

8.5 Conclusions

There is general consent that tumours are frequent in the elderly and that elderly individuals have an impaired immune response. These comparisons are usually performed comparing average young and middle-age individuals to the elderly. However, only a few researchers have compared healthy elderly individuals with aged patients with cancer and elderly cancer patients with comorbidities [37]. In general, healthy old individuals have an excellent protective immune response mostly dependent upon pro-inflammatory cells and mediators, which are clinically silent. A good memory response may protect these individuals from tumour appraisal or reappraisal.

On the contrary, in elderly patients with comorbidities, the protective response may be impaired, and tumour appearance and reappraisal increase dramatically. Up-to-date, it is difficult to distinguish if the group with comorbidities is more susceptible to develop tumours and why. Pharmacological therapy can play a role in increasing the risk to develop cancer.

Most of the clinical trials with different therapeutic schemes are usually not performed in elderly individuals. The pharmacokinetics and pharmacodynamics of many compounds are calculated in clinical trials that usually includes young and middle-aged people. Then, the recommended doses may produce toxic effects in the elderly. Besides the fact that unadjusted drug concentrations can be detrimental cell
metabolism or to immune response, drug interactions may not be appropriately addressed.

The use of chemotherapy and checkpoint inhibitor therapy should be strictly monitored in the elderly population, especially in the presence of comorbidities. The addition of coadjuvant therapy should be carefully analysed depending on the individual. Finally, more research is required on the field in order to provide the critical guidelines required. In the recent COVID 19 outbreak, we have learned how many elderly people different countries have and how susceptible elderly populations are to infections. However, many people have not understood that this population is increasing rapidly. It represents a challenge that must be resolved.

References

1. DeSantis CE, Miller KD, Dale W et al (2019) Cancer statistics for adults aged 85 years and older. 2019. CA Cancer J Clin 69(6):452–467
2. Siegel RL, Miller KD, Jemal A (2016) Cancer statistics 2016. CA Cancer J Clin 66:7–30
3. Goldberg EL, Shaw AC, Montgomery RR (2020) How inflammation blunts innate immunity in aging. Interdiscip Top Gerontol Geriatr 43:1–17
4. Vatic M, von Haehling S, Ebner N (2020) Inflammatory biomarkers of frailty. Exp Gerontol 133:110858
5. Pansarasa O, Pistono C, Davin A et al (2019) Altered immune system in frailty: genetics and diet may influence inflammation. Ageing Res Rev 54:100935
6. Cerezo D, Peña MJ, Mijares M, Martínez G, Blanca I, De Sanctis JB (2015) Peptide vaccines for cancer therapy. Recent Patents Inflamm Allergy Drug Discov 9(1):38–45
7. Bektas A, Schurman SH, Sen R, Ferrucci L (2017) Human T cell immunosenescence and inflammation in aging. J Leukoc Biol 102(4):977–988
8. Gattinoni L, Lugli E, Ji Y, Pos Z, Paulos CM, Quigley MF, Almeida JR, Gostick E, Yu Z, Carpenito C et al (2011) A human memory T cell subset with stem cell-like properties. Nat Med 17(10):1290–1297
9. Park SY, Nam JS (2020) The force awakens: metastatic dormant cancer cells. Exp Mol Med 52(4):569–581. https://doi.org/10.1038/s12276-020-0423-z
10. Nicolini A, Rossi G, Ferrari P, Carpi A (2020) Minimal residual disease in advanced or metastatic solid cancers: the G0-G1 state and immunotherapy are key to unwinding cancer complexity. Semin Cancer Biol. S1044-579X(20)30075-4
11. Belgioia L, Desideri I, Errico A et al (2019) Safety and efficacy of combined radiotherapy, immunotherapy and targeted agents in elderly patients: a literature review. Crit Rev Oncol Hematol 133:163–170
12. Hurria A, Togawa K, Mohile SG et al (2011) Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol 29(25):3457–3465
13. Postow MA, Sidlow R, Hellmann MD (2018) Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med 378(2):158–168
14. Helissey C, Vicier C, Champiat S (2016) The development of immunotherapy in older adults: new treatments, new toxicities? J Geriatr Oncol 7(5):325–333
15. Feliu J, Jiménez-Munárriz B, Basterretxea L et al (2020) Predicting chemotherapy toxicity in older patients with cancer: a multicenter prospective study. Oncologist 10:1634
16. De Sanctis JB, Garmendia JV (2015) Vaccine therapy update for pregnant, immunocompromised, and chronic diseases patients. Recent Patents Inflamm Allergy Drug Discov 9(1):46–53
17. Huang Y, Chen Z, Wang H et al (2020) Follicular regulatory T cells: a novel target for immunotherapy? Clin Transl Immunol 9(2):e1106
18. Ayroldi E, Cannarile L, Adorisio S, Delfino DV, Riccardi C (2018) Role of endogenous glucocorticoids in cancer in the elderly. Int J Mol Sci 19(12):3774
19. Inokawa H, Umemura Y, Shimba A et al (2020) Chronic circadian misalignment accelerates immune senescence and abbreviates lifespan in mice. Sci Rep 10(1):2569
20. Souquette A, Frere J, Smithey M, Sauce D, Thomas PG (2017) A constant companion: immune recognition and response to cytomegalovirus with aging and implications for immune fitness. Geroscience 39(3):293–303
21. van den Berg SPH, Pardieck IN, Lanfermeijer J et al (2019) The hallmarks of CMV-specific CD8 T-cell differentiation. Med Microbiol Immunol 208(3–4):365–373
22. Merani S, Pawelec G, Kuchel GA, McElhaney JE (2017) Impact of aging and cytomegalovirus on immunological response to influenza vaccination and infection. Front Immunol 8:784
23. Berry R, Watson GM, Jonjic S, Degli-Esposti MA, Rossjohn J (2020) Modulation of innate and adaptive immunity by cytomegaloviruses. Nat Rev Immunol 20(2):113–127
24. Haanen JBAG, Carbonnel F, Robert C et al (2018) Management of toxicities from immunotherapy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 29(Suppl 4):iv264–iv266
25. Pereira MP, Ständer S (2018) Therapy for pruritus in the elderly: a review of treatment developments. Expert Opin Pharmacother 19(5):443–450
26. Russell B, Moss C, George G et al (2020) Associations between immune-suppressive and stimulating drugs and novel COVID-19-a systematic review of current evidence. Ecancermedicalscience 14:1022
27. Agius L, Ford BE, Chachra SS (2020) The metformin mechanism on gluconeogenesis and AMPK activation: the metabolite perspective. Int J Mol Sci 21(9):E3240
28. Zhao B, Luo J, Yu T, Zhou L, Lv H, Shang P (2020) Anticancer mechanisms of metformin: a review of the current evidence. Life Sci 2020:117717
29. Tseng CH (2017) Metformin and lung cancer risk in patients with type 2 diabetes mellitus. Oncotarget 8(25):41132–41142
30. Grivennikov SI, Greten FR, Karin M (2010) Immunity, inflammation, and cancer. Cell 140(6):883–899
31. van Niekerk G, Christowitz C, Conradie D, Engelbrecht AM (2020) Insulin as an immunomodulatory hormone. Cytokine Growth Factor Rev 52:34–44
32. Zeiser R (2018) Immune modulatory effects of statins. Immunology 154(1):69–75
33. Yao H, He G, Yan S et al (2017) Triple-negative breast cancer: is there a treatment on the horizon? Oncotarget 8(1):1913–1924
34. Hu YB, Hu ED, Fu RQ (2018) Statin use and cancer incidence in patients with type 2 diabetes mellitus: a network meta-analysis. Gastroenterol Res Pract 2018:8620682
35. Soria-Castro R, Schcolnik-Cabrera A, Rodriguez-Lopez G et al (2019) Exploring the drug repurposing versatility of valproic acid as a multifunctional regulator of innate and adaptive immune cells. J Immunol Res 2019:9678098
36. Perucca E, Grimaldi R, Gatti G, Pirracchio S, Crema F, Frigo GM (1984) Pharmacokinetics of valproic acid in the elderly. Br J Clin Pharmacol 17(6):665–669
37. Denson AC, Mahipal A (2014) Participation of the elderly population in clinical trials: barriers and solutions. Cancer Control 21(3):209–214