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A brief overview of cancer research in the elderly population

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SUMMARY

Cancer is a complex disease and numerous treatments have been proposed and used. The breakthrough has been the use of biological therapy with checkpoint inhibitors, decreasing tumor burden. The life expectancy of cancer patients has increased. However, the major problem refers to the high incidence of tumors in the elderly population most of which have comorbidities. The number of healthy aged individuals is low, and usually, clinical trials do not take into account, aged individuals. Therefore, the rationale of tumor therapies in the elderly population is very complex. One interesting initiative is to analyze cancer incidence and survival of a large cohort of individuals that have taken specific therapies for a number of years. The review will focus on three drugs: valproic acid, disulfiram (Antabuse), and metformin. In this short review, we will give some insights into the importance of these drugs in cancer therapy in general and in the aged population.

Key words: *Cancer, immune response, elderly population, valproic acid, disfulfiram, metformin*

RESUMEN

El cáncer es una enfermedad compleja en el cual se han utilizado numerosos tratamientos. El mayor avance en tratamiento ha sido el uso de inhibidores de puntos de control, disminuyendo la carga tumoral. La esperanza de vida de los pacientes con cáncer ha aumentado. Sin embargo, se mantiene la alta incidencia de tumores en la población longeva, la mayoría de los cuales tienen comorbilidades. El número de ancianos saludables es bajo y, por lo general, los ensayos clínicos no tienen en cuenta a los ancianos. Por lo tanto, el uso de terapias tumorales en la población de edad avanzada es muy compleja. Una iniciativa es analizar la incidencia de cáncer y la sobrevida de una cohorte de individuos que han tomado terapias específicas durante varios años. La revisión se centrará en tres medicamentos: ácido valproico, disulfiram (Antabuse) y metformina. En esta revisión, disertaremos sobre la importancia de estos medicamentos en la terapia contra el cáncer en general y en la población de edad avanzada.

Palabras clave: *Cáncer, respuesta inmune, ancianos, ácido valproico, disulfiram, metformina*

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In memoriam of Drs. Luigi Varesio and Igor Espinoza-Delgado.

INTRODUCTION

Cancer has been defined in general dictionaries as "a disease caused by an uncontrolled division of abnormal cells in a part of the body". Such a broad

definition does not give the reader an insight into disease complexity or the whereabouts of cancer risk or therapies. For many years the researchers have made enormous efforts to unravel pieces of the mysterious disease, and lately, those efforts lead to an increase in patient survival (1-2). The main change for this success was to understand the patient´s immune response, tumor heterogeneity, genetic instability, cellular stress, cell death, and cell dormancy (3-4). In 2018 and 2019, the Nobel prizes were given to researchers that had worked on immune therapy, Allison J, Honjo T (checkpoint inhibitors), and hypoxia, Kaelin KG, Ratcliffe PJ, Semenza GL. These two topics dramatically changed the understanding of tumors biology and microenvironment.

The first and most challenging issue was to understand that biological immune therapy was able to generate an effective immune response in patients that did not have any other therapeutic option (5). The treatment was able to induce antigen presentation in cold tumors (table 1) and consequently, facilitate tumor elimination by cytotoxic immune cells (6). Since the majority of the tumors are heterogenous, this therapy enhances the probability of tumor elimination and decreases the possibility of metastasis (5-6). However, not all patients respond to the treatment; young individuals respond better than older individuals. In aged individuals, the use of biological therapy is generally contraindicated based upon comorbidities, impaired drug clearance, and high inflammatory responses that require the use of steroids (7). The other important issue is the high cost which can not be covered by the patient. In summary, new therapies are required for elderly individuals.

Cancer in the elderly population

The increased susceptibility to infections in the elderly is an indication of an impaired innate immunity which leads to a decreased response of adaptive immunity (8-10). It is expected that aging will predispose individuals to a less anabolic and catabolic activity limiting the response of cells and tissue to injuries. One biological mechanism that partially compensates this phenomenon is inflammaging (8-10). Inflammaging is defined as a dynamic protective response in which pro-inflammatory mediators and circulating primed cells are increased without generating a clinically perceptible inflammation (8). This pro-inflammatory response is a quick adaptative response observed in healthy elderly individuals. It is often underestimated, it could be modified by therapy, and it partially protects from tumor growth (11). Therapeutic management of inflammaging is now an important field of research.

The incidence of cancer in the elderly has always been a matter of discussion (2-4). Cancer is frequently diagnosed in the elderly, with approximately 50 % of patients being over 70 years of age (2-4). According to the British cancer organization, female rates of cancer are lower than males after 75 years, and there is a drop in cancer incidence after 85 years (4). Either tumor screening is decreased after 75 years or healthy elderly individuals that have an efficient immune response live longer and dye of other natural causes.

In the aged population, one of the most common cancer in males is prostate cancer and in women breast cancer; however, in both genders, the second most common is lung cancer (4). Solid tumor growth is generally slow in the elderly population that did not have a clinical history of neoplasm. These patients may respond to standard therapy until the tumor becomes resistant and metastasize. At his stage, immunological therapies usually are not indicated due to the high costs, the number of secondary effects, the high probability of metastasis, and the low probability of decreasing tumor burden.

Patients that had an incipient or surgical removed tumor may present new and aggressive tumor growth in the same organ or other organs due to the reactivation of dormant metastatic cells that have not been contained by the immune system (12). This late group is now carefully monitored by the oncologists due to the marked increase in documented cases (13). Management of these patients may be complicated due to the high comorbidities (14-16). However, some groups are managing biological therapy in patients with low comorbidities to increase cancer survival (17-18). More research is needed in this area (18).

In the case of lung cancer and chronic

obstructive pulmonary disease (COPD) there has been a long discussion on the origin and incidence of both diseases (19). The prevalence of COPD is between 12-20 % in the elderly population, and the increase of patients with both diseases is increasing (20). Both diseases are complex to treat and survival depends on the severity of COPD (20).

Hematologic tumors are also prevalent in the elderly population (21). One of the hypotheses in geriatric oncology is that continuous replacement of circulating immune cells from the bone marrow, impaired genetic control mechanisms, and the absence of thymic selection increases the probability of generating tumor cells. Patients with mild immune deficiencies and some with acquired immunodeficiencies are prone to develop B cell lymphoma or myeloma (22). Others to a minor extent, develop monocytic leukemia (21).

Medical screening of the aged population has proven to be very useful (22). The results of the screening have allowed clinical researchers to estimate cancer incidence and cancer risks in different populations (23). However, more research is needed to decrease cancer incidence and increase patient survival.

Drug screening in populations, cancer incidence, and cancer therapy

One of the most exciting approaches in documented medical files is the analysis of the population for a long time. Epidemiological relevant data on morbidities, treatment, and mortality allows researchers to generate guidelines that are useful for the general population. These databases permitted the researchers to analyze the incidence of tumors, therapy, and survival. In general, for a classified tumor, statistical data is available. However, Danish epidemiologists were amazed by the fact that significant differences in patient survival with large cohorts were observed in several cases (22). We will briefly outline three drugs encountered that are now being screened in clinical trials and can be useful in aged individuals.

The first case was documented for valproic acid, which is commonly used as anticonvulsive therapy that appeared in the French market in the late 1960s (23). The association between the use of valproic acid (VA) and breast cancer survival came after the mechanism of action of this compound was established (24). VA inhibits histone deacetylases and consequently inhibits germinal mutations which decrease tumor heterogeneity (23-24). Moreover, VA inhibits the effect of vascular endothelial growth factor in the tumor milieu (25). VA is now used as adjuvant therapy in several cancers (26), and there are several clinical trials ongoing (26). Even though more research is needed, the use of low doses of VA in elderly patients is generally well tolerated (27-28). VA also modulates the immune response enhancing the response to pathogens and decreasing autoimmune disease and hypersensitivity responses (29). In the new field of allergic-oncology, VA may be a useful adjuvant therapy in paraneoplastic manifestations (30).

The second case is disulfiram, Antabuse, a drug used to treat alcoholism (31). Disulfiram is a drug that has been used since the late 1930s and patients that have used disulfiram for long periods have less incidence and higher survival of breast cancer (32). Its major metabolite diethyldithiocarbamate (DTC) avidly binds Copper generating a complex (CuEt) which has been shown to be cytotoxic to a wide variety of tumors *in vivo* and *in vitro* (32-33). The mechanism of action of the compound has been published (33). Currently, there are several clinical trials using disulfiram and Copper, and hopefully, new developments will provide evidence of the role of different metabolites in cancer response.

Metformin is an old drug, proposed initially as an antimalarial drug in the 1940s, usually used for the treatment of type 2 diabetes (since 1957). Patients that used metformin had a higher survival of cancer (35). Several groups postulated that the metabolic effect of metformin on glucose metabolism affects cancer growth (36). These effects on glucose catabolism seem to potentiate the immune response (37,38). Metformin has been involved in several clinical trials as an adjuvant for tumor therapy (39,40).

The contamination of several batches of long term release metformin with the pro-cancer metabolite N-Nitrosodimethylamine (NDMA), has raised concerns in the general population;

however, the basic drug seems to contain very low amounts of the contaminant (https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-metformin). Glipizide, a similar drug to metformin, was also shown to inhibit cancer growth (41). More research is needed in the area to establish the importance of glipizide as an adjuvant in anti-tumor therapy.

Pharmacological research is needed to analyze different structures of the drugs mentioned above to increase biological activity either enhancing immune response, decreasing tumor burden, or both and increasing drug safety in the elderly population.

Table 1

Differences between hot and cold tumors

	Cold	Hot
Biological characteristics	Less differentiated cells	Antigen expression. PD-1 expression
	Stem cell-like cells	Differentiated cells
	Mesenchymal like cells	The tumor expresses normal proteins in the cell membrane.
	Active beta-catenin signaling	Suppressed beta-catenin signaling
	Epigenetic silencing	Epigenetic programming
	Low somatic mutation	High somatic mutation
	Low germinal mutation	High germinal mutation
	P-glycoprotein expression	Low expression of P-glycoprotein
Immunological characteristics	Enriched suppressive cytokines	Enriched Th1 cytokines in the tumor milieu
	Expression of KIR inhibitory receptors	Tumors express ligands of killing receptors.
	Tumours are surrounded by Myeloid suppressive cells, Treg cells, and dysfunctional CD8 cells, NK cells, and Th1 cells.	A high number of effector cells CD8, NK, and Th1. Presence of functional antigen-presenting cells.

General Conclusions

Even though biological immune therapy can be useful to treat most cancers, the treatment is not always successful, especially in the elderly population. Probably, the inflammaging observed in aged individuals may be responsible for the incidence of secondary effects.

Several drugs have been in the market for several years, which can be used as adjuvant therapy for cancer treatment in general. The important issue with the drugs reviewed is that safety in all ages has been evaluated in old drugs and they can be safely used in the elderly population. These drugs intend to be used ad adjuvant therapy in elderly cancer patients in which common cancer treatment should be adjusted and monitored very closely. Taking into account that around 15 % of the world population is above 60 years old, the effort for new therapeutic schemes is urgently needed.

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