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IMMUNOTHERAPY IN CANCER PATIENTS IN COVID-19 ERA

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The coronavirus disease 2019 pandemic is concerning for patients with cancer who are receiving immunotherapy. COVID-19 has had a major impact on cancer and clinical trials, affecting treatment and oncology patients in a number of different ways. Immunotherapy has also been found to have a durable treatment response in patients after just a few courses of therapy, for example in cases where patients can't continue with their treatment. The drugs reveal the cancer to the body's immune system, turning it against the cancer and, when treatment stops, the immune system can continue killing the cancer itself. Uncertainty remains about whether immunotherapies increase the risk of infection with severe acute respiratory syndrome Coronavirus 2 or increase the risk of severe disease and death upon infection.

Keywords: immunotherapy, cancer, COVID-19, infection, immune system.

INTRODUCTION

Immunotherapy is a treatment based on the manipulation of the immune system in order to eliminate a pathogen or a transformed cell. Cancer immunotherapy is therefore a biotherapy that uses the immune system to specifically eliminate the tumor cells while trying to limit damage to surrounding healthy cells. Many immunotherapy protocols have been developed in recent years and are increasingly used in addition to other treatments (surgery, chemotherapy, radiotherapy ...) in many types of cancer such as melanoma (Margolin, 2016), Renal carcinoma (Curtis *et al.*, 2016) or glioblastoma (Tivnan *et al.*, 2017). Current immunotherapy strategies are based on two main principles. Active immunotherapy which involves stimulating the patient's immune system so that it reacts again against tumor cells. Passive immunotherapy, when for her, is linked to the transfer of components of the immune system to patients so that they directly destroy the targeted tumor cells. Several degrees of complexity in addition to these different immunotherapy approaches when using the system immune system of the patient (autologous) or that of another individual (allogeneic) and depending of the targeted antigen (s). COVID-19 is the abbreviation for "Coronavirus Disease 2019", a disease caused by a new rapidly spreading coronavirus called SARS-CoV-2. Coronaviruses are a family of viruses that cause disease in mammals and birds, but can occasionally develop and infect humans. The first human cases of COVID-19 from SARS-CoV-2 were reported in Wuhan, China, in December 2019. In this guide, SARS-CoV-2 will be referred to simply as "coronavirus". Coronaviruses are spherical in shape and are provided with spike (pointed) proteins that protrude from their surface. These proteins are able to bind to human cells allowing the viral particle to bind to them. At this point, the virus's genes can enter the human cell and multiply to produce new viruses. In humans, coronaviruses cause respiratory infections. The new coronavirus (SARS-CoV-2) has spread rapidly around the world, and the disease resulting from infection with the virus, COVID-19, can cause serious and life-threatening infections, especially in the elderly advanced age (e.g. age over 65 years) and in those with other underlying diseases.

ANTI-TUMOUR IMMUNOTHERAPY

PRESENTATION OF THE IMMUNE SYSTEM

The immune system is made up of a set of cellular and molecular effectors capable of recognizing and eliminating both foreign pathogens and altered Self cells. There are two major components to the system immune: innate

immunity and adaptive immunity. Innate immunity is the body's first line of defence. It brings together molecular actors such as complement and cellular actors such as granulocytes (basophils, eosinophils and neutrophils), monocytes, macrophages, cells dendritic (DC) or NK (Natural Killer) cells. These different components allow rapid (few hours) but unspecific recognition of pathogens. Adaptive immunity takes longer to develop (a few days) but is highly specific pathogen target. It is composed of two major cellular effectors: LT (T lymphocytes) and LB (B lymphocytes). These cells are able to target antigens specific to the target pathogen and set up a memory in order to react more quickly in case of new infection. However, other cell types have hybrid profiles and cannot belong than to either of these immunities. An intermediate category allows these to be grouped together cells, called transitional immunity because it is located at the interface between innate immunity and adaptive. Natural Killer T cells and LT γδ are among them (Dranoff, 2004). Their rate of reaction to pathogens is close to that of immunity innate while their effector functions are rather close to those of immunity adaptive.

ROLE OF THE IMMUNE SYSTEM IN CANCER

The main function of the immune system is to defend the body against intrusion pathogens, via the recruitment of many complementary immunity actors innate and adaptive immunity. However in some cases, the immune system can react against the host especially in autoimmune diseases. In the case of cancer, the immune system must react against cells in the body that have become abnormal and the eliminate to prevent them from altering the functions of the tissue / organ from which they are derived. The existence of immuno-surveillance, a phenomenon of monitoring the appearance of cells transformed / tumor by the immune system, has been shown in different pathophysiological situations. Patients with immunosuppression, for example in the case of taking immunosuppressants following an organ transplant, or a immunodeficiency, as in the case of an HIV infection (immunodeficiency virus) have an increased incidence of cancer development (Dunn *et al.*, 2004). 13 In addition, the presence of TIL (tumor infiltrating lymphocytes) in cancer patients can lead to the development of a spontaneous anti-tumor immune response and can also serve as a prognostic indicator of patient survival in many cancers (melanoma, ovarian cancer…) (Burton *et al.*, 2011; Dunn *et al.*, 2004; Sato *et al.*, 2005). The immune system is involved in various processes during prevention and cancer development. Even before a tumor grows, it protects the body against pathogens, including viruses that may have a risk factor for cell transformation and lead to the development of viro-induced tumors (Schreiber *et al.*, 2011). If a tumor begins to grow, it removes the tumor cells present and also contributes to the reduction of inflammation that can lead to implantation of a microenvironment that promotes tumor growth (Schreiber *et al.*, 2011).

TUMOR IMMUNO-EDITING CONCEPT

Studies in murine models have found that tumors develop in immunodeficient mice are more immunogenic than mouse-derived tumors immunocompetent (Shankaran *et al.*, 2001). Following these observations, the concept immunosurveillance was revised and the notion of tumor editing was introduced. Indeed, the immune system by reacting against tumor cells then modifies their immunogenicity (Dunn *et al.*, 2002). The concept of tumor immuno-editing, also called "3 E rule" is broken down into 3 steps (Schreiber *et al.*, 2011): – Elimination: during this phase, the entire immune system (innate and adaptive) detects and destroys tumor cells before tumor formation clinically detectable. – Equilibrium: At this stage, very few tumor cells survived the phase d'elimination. The adaptive immune system keeps tumor cells in a quiescent state by controlling their proliferation. It is during this phase, who can last for several years,that the immunogenicity of the tumor is most impacted. – Exhaust: after a certain time of selective pressure by the system immune, some tumor cells will be able to bypass their recognition by him. They will then proliferate to form a tumor clinically detectable.

The transition between the equilibrium phase and the exhaust phase can be caused by a change in tumor cell immunogenicity related to selection pressure exerted by the immune system or by an alteration of the immune system related to the implementation of place of an immunosuppressive microenvironment by tumor [van der Burg *et al.*, 2016). Indeed, tumor cells can alter the phenotype and functions of the cells that surround them to make them immunosuppressive or pro-tumor (eg Treg (LT regulators)], via the secretion of immu-

nosuppressive cytokines (eg IL-10 (interleukin 10), TGF-β (transforming growth factor β). It is also possible that external factors allow to tumor cells to enter directly into equilibrium or even escape phase without follow the first steps, especially during high environmental stress or in some case of immunodeficiency.

PRINCIPLE AND CLASSIFICATION OF TUMOR IMMUNOTHERAPY

Immunotherapy is a treatment that is based on manipulating the immune system in order to eliminate a pathogen or a transformed cell. Anti-cancer immunotherapy is therefore a biotherapy that uses the immune system to specifically eliminate the tumor cells while trying to limit damage to surrounding healthy cells. Many immunotherapy protocols have been developed in recent years and are increasingly used in addition to other treatments (surgery, chemotherapy, radiotherapy…) in many types of cancers such as melanoma (Margolin, 2016), renal carcinoma (Curtis *et al.*, 2016) or glioblastoma (Tivnan *et al.*, 2017). Current immunotherapy strategies are based on two main principles. Active immunotherapy which is to stimulate the patient's immune system so that it reacts again against tumor cells. Passive immunotherapy, quant to her, is related to the transfer of components of the immune system to patients so that they directly destroy targeted tumor cells . Several degrees of complexity are added to these different immunotherapy approaches as they use the system immune system of the patient (autologous) or that of another individual (allogeneic) and in function of the targeted antigen.

ACTIVE IMMUNOTHERAPY

As mentioned above, the goal of active immunotherapy is to stimulate the system immune system to promote a response directed against tumor cells. Several methods, specific or not, have been developed and are presented below.

IMMUNOMODULATORY ANTIBODIES

The most developed immunotherapy currently is based on the use of targeted antibodies against immune system checkpoints. These checkpoints are essential for regulating the immune response. They play one key role in maintaining tolerance to the body's cells and in inhibition cellular effectors to control the duration and intensity of the inflammatory reaction (Keir *et al.*, 2008). Thus in many cancers, tumor cells overexpress them ligands of these inhibitory molecules to prevent activation of the immune system against them (Pardoll, 2012).

Several ligand/inhibitor molecule pairs are involved in immunosuppression by tumor cells . Among them, CTLA-4 (cytotoxic T lymphocyte associated protein 4) and PD1 (programmed cell death 1) are two particularly inhibitory molecules targeted (Pardoll, 2012). CTLA-4 is a competitive inhibitor of the CD28 activator receptor, expressed by LTs. They both have the expressed CD80 / CD86 molecules as ligands by CPAs (antigen presenting cell) or target cells, but CTLA-4 has a better affinity than CD28 for these ligands (Chambers *et al.*, 2001). CTLA-4 is expressed during LT activation and its high affinity for its ligands will promote their interaction, leading to an end to the proliferation and differentiation of LTs (Chambers *et al.*, 2001). PD1 is also expressed on the surface of activated LTs and has two ligands: PDL1 and PDL2 (programmed cell death ligand 1 and 2), which are expressed by CPAs and often overexpressed by tumor cells (Freeman *et al.*, 2000). As with CTLA-4, the interaction of PD1 with its ligands leads to inhibition of proliferation and production of pro-inflammatory cytokines by LTs. It also induces effector LT apoptosis while decreasing that of regulatory LTs, which promotes immunosuppression of the tumor microenvironment (Freeman *et al.*, 2000). Tumor cells, via expression ligands of these inhibitory molecules, can therefore limit activation and function LT effectors

Different antibodies have therefore been developed to prevent the interactions of these couples receptors / ligands, allowing activator LT activation and cell destruction tumors (Pardoll, 2012). Thus, antibodies inhibiting these control points such as ipilimumab, an anti-CTLA-4 antibody, or nivolumab, an anti-PD1 antibody, have been shown to their efficacy in various cancers, including melanoma (Hodi *et al.*, 2010) and breast cancer lung (Rizvi *et al.*, 2015). Although their effectiveness has been demonstrated in different types of cancers, some patients remain refractory to this type of immunotherapy. That's why new inhibitory antibodies other control points such as LAG-3 (lymphocyte activation gene 3), TIGIT (T cell immunoreceptor with Ig and ITIM

domains) or Tim-3 (T cell membrane protein 3) were developed and are being evaluated (Velcheti and Schalper, 2016).

Numerous studies also focus on the development of activating antibodies in targeting LT costimulation molecules, such as 4-1BB, OX40 or CD40 (Velcheti and Schalper, 2016). However, these strategies have a drawback development of autoimmune toxicity (eg colitis, neurological impairment) which may require discontinuation of treatment (Juszczak *et al.*, 2012; Zimmer *et al.*, 2016).

ANTI-TUMOR VACCINATION

Therapeutic vaccination as part of anti-tumor immunotherapy provides induction an endogenous immune response specifically targeting tumor cells. First of all, as part of the prevention of virus-induced cancers, some vaccines that have not been developed for the treatment of cancers can be used, such as the HPV vaccine (human papillomavirus) for cervical cancer (Schiller and Müller, 2015). Then, different strategies were considered to activate the immune system patients through different sources of tumor antigens, in order to specify this response: des peptides or proteins expressed by tumor cells can be used after purification or synthesis; cell mixtures (healthy and / or tumor cells) or lysates obtained from cells that may come from fresh or frozen samples from tumors or tumor lines, autologous or allogeneic (Butterfield, 2015) . The most widely used anti-tumor vaccination strategy is DC administration. En effect, DCs are the most effective immune cells for presenting antigens and activate LT αβ CD4 +, CD8 + and NK cells (Gustafsson *et al.*, 2011). Most often, the DCs are differentiated, ex vivo, from monocytes present in PBMCs (peripheral blood mononuclear cells) cultured in the presence of IL-4 and GM-CSF (macrophage granulocyte colony stimulating factor).

IMMUNOMODULATORY MOLECULES

An approach also used to stimulate the response in a global and direct way immune function is the use of cytokines, such as IFNs (interferon) type I which allow maturation of DCs and activation of immune effectors (LT, NK) or IL-2 for amplify LTs (Velcheti and Schalper, 2016). However, the use of these cytokines remains very delicate due to their lack of specificity and the many side effects they have déclenchent. For example, following systemic injections of IL-2, nonspecific activation of the system. Immune system, mainly LT, leads to a massive release of proinflammatory cytokines called “cytokine storm”. The most common side effects are fever, malaise, digestive disorders and in some cases the consequences can be fatal to patients (Dhupkar and Gordon, 2017). Still with the goal of restoring an immune response directed against tumor cells, other, less direct strategies have been developed. This is the case with inhibitors of the metabolism that target the immunosuppressive microenvironment set up by the tumour. For example, inhibitors of the enzyme IDO (indoleamine-2,3-dioxygenase) have been developed with the aim of decreasing the immunosuppression it engenders (Amobi *et al.*, 2017). Indeed, IDO is involved in the breakdown of tryptophan, an essential amino acid, and is overexpressed in many types of cancers. This results in a metabolic disorder characterized by local depletion of tryptophan and accumulation of its derivatives, promoting immunosuppression (Amobi *et al.*, 2017).

PASSIVE IMMUNOTHERAPY

Unlike active immunotherapy, passive immunotherapy is based on the transfer of of immune system component (s) to directly destroy tumor cells.

THERAPEUTIC ANTIBODIES

In the context of passive immunotherapy, the use of antibodies is aimed at the death of tumor cells by different immune mechanisms (ADCC) mediated cytotoxicity), complement) and nonimmune (direct lysis) (Buss *et al.*, 2012). To subtlety of this type of treatment is based on the specificity of the antibody targeted by the antibodies. Thus, two categories of antigens are distinguished: tumor-specific antigens, expressed exclusively by tumor cells, and tumor-associated antigens, which they are expressed by both tumor cells and healthy tissue but in ways different (overexpression, mutation…). The ideal is to be able to target a specific antigen of the tumor to prevent the attack of healthy tissue but the identification of this type of antigen remains rare because they are often expressed heterogeneously within the tumor and poorly conserved from the made of induced selective pressure.

ADOPTIVE CELL THERAPY

Adoptive cell therapy is based on the administration of immune effectors cytotoxic to patients, to directly destroy the tumor, without seeking to induce endogenous immune response. Different lymphocyte populations (eg LT αβ, LT γδ, NK) can be used but they must share common characteristics: a specificity for a tumor antigen, robust effector functions, and good capacity amplification (Rosenberg and Restifo, 2015).

Generally, this strategy requires the manipulation of these ex vivo effectors in order to select according to their antigenic specificity and / or amplify them (Figure 1). These cells can therefore come directly from the intra-tumor infiltrate, the lymph nodes draining the tumor or peripheral blood (Rosenberg and Restifo, 2015). The first adoptive cell therapy was implemented by Rosenberg and his collaborators, in patients with melanoma (Rosenberg *et al.*, 1988). Tumor regression may have be observed in several patients by injection of autologous TIL, after amplification ex vivo in the presence of IL-2. In order to improve the therapeutic potential of this therapy, it is possible to sort the LTs of the patients for their antigenic specificity and / or to amplify them ex vivo in the presence of a antigen of interest (Rosenberg and Restifo, 2015).

IMMUNE RESPONSES TO SARS-COV-2

Immune response to SARS-CoV-2 involves both cell-mediated immunity and antibody production.

CELL-MEDIATED IMMUNE RESPONSE

T-cell responses against the SARS-CoV-2 spike protein have been characterised and correlate well with IgG and IgA antibody titres in COVID-19 patients, which has important implications for vaccine design and long-term immune response [Grifoni *et al.*, 2020; Weiskopf *et al.*, 2020; Braun *et al.*, 2020]. It is currently unknown whether antibody responses or T-cell responses in infected people confer protective immunity, and if so, how strong response is needed for this to occur. CD8+ T cells are the main inflammatory cells and play a vital role in virus clearance. Total lymphocytes, CD4+ T cells, CD8+ T cells, B cells, and natural killer cells showed a significant association with inflammatory status in COVID-19, especially CD8+ T cells and CD4+/CD8+ ratio [Wang *et al.*, 2020]. Decreased absolute numbers of T lymphocytes, CD4+ T cells, and CD8+ T cells were observed in both mild cases and severe cases, but accentuated in the severe cases. In multivariate analysis, post-treatment decrease in CD8+ T cells and B cells and increase in CD4+/CD8+ ratio were indicated as independent predictors of poor treatment outcome [Wang *et al.*, 2020]. The expression of IFN-γ by CD4+ T cells also tends to be lower in severe cases than in moderate cases [Chen *et al.*, 2020].

Studies have shown that patients with cancer and COVID-19 have suggested a high mortality rate compared to the general population. Patients with lung cancer are more prone to COVID-19 given their older age, smoking habits, and pre-existing cardiopulmonary comorbidities, in addition to cancer treatments.

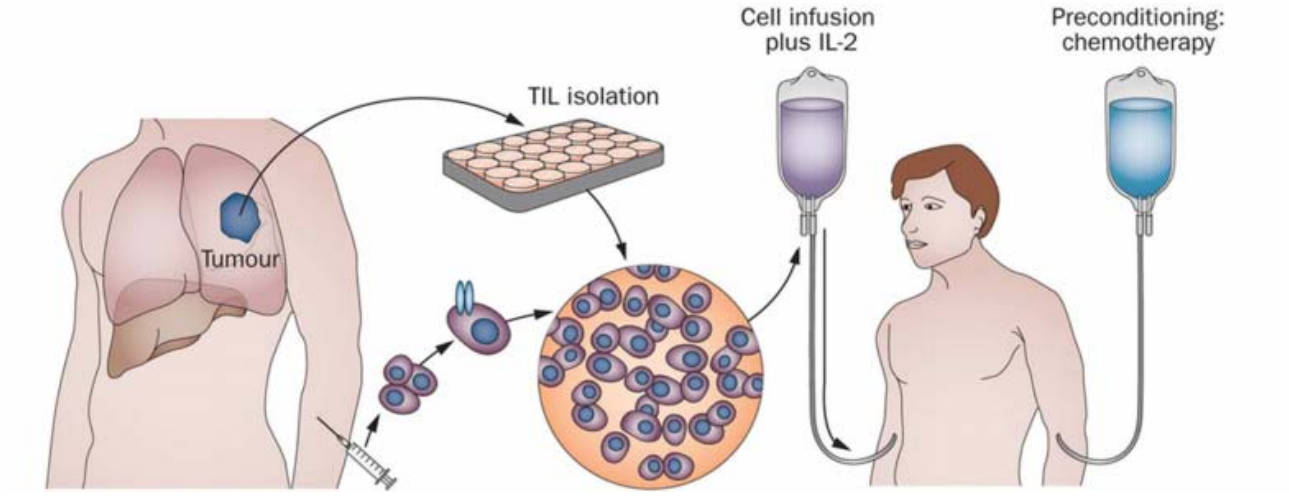

Figure 1. Different strategies of adoptive cell therapy.
Source: Adaptated after Rosenberg et Restifo, 2015.

Chemotherapy was an additional risk factor for the development of COVID disease compared to immunotherapy or target therapy, according to the TERAVOLT study [Whisenant *et al.*, 2020].

CONCLUSIONS

Even though cancer immunotherapy is not intended to treat infections, we think it has the same vector and works in the same direction towards boosting the patient's immune system.

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